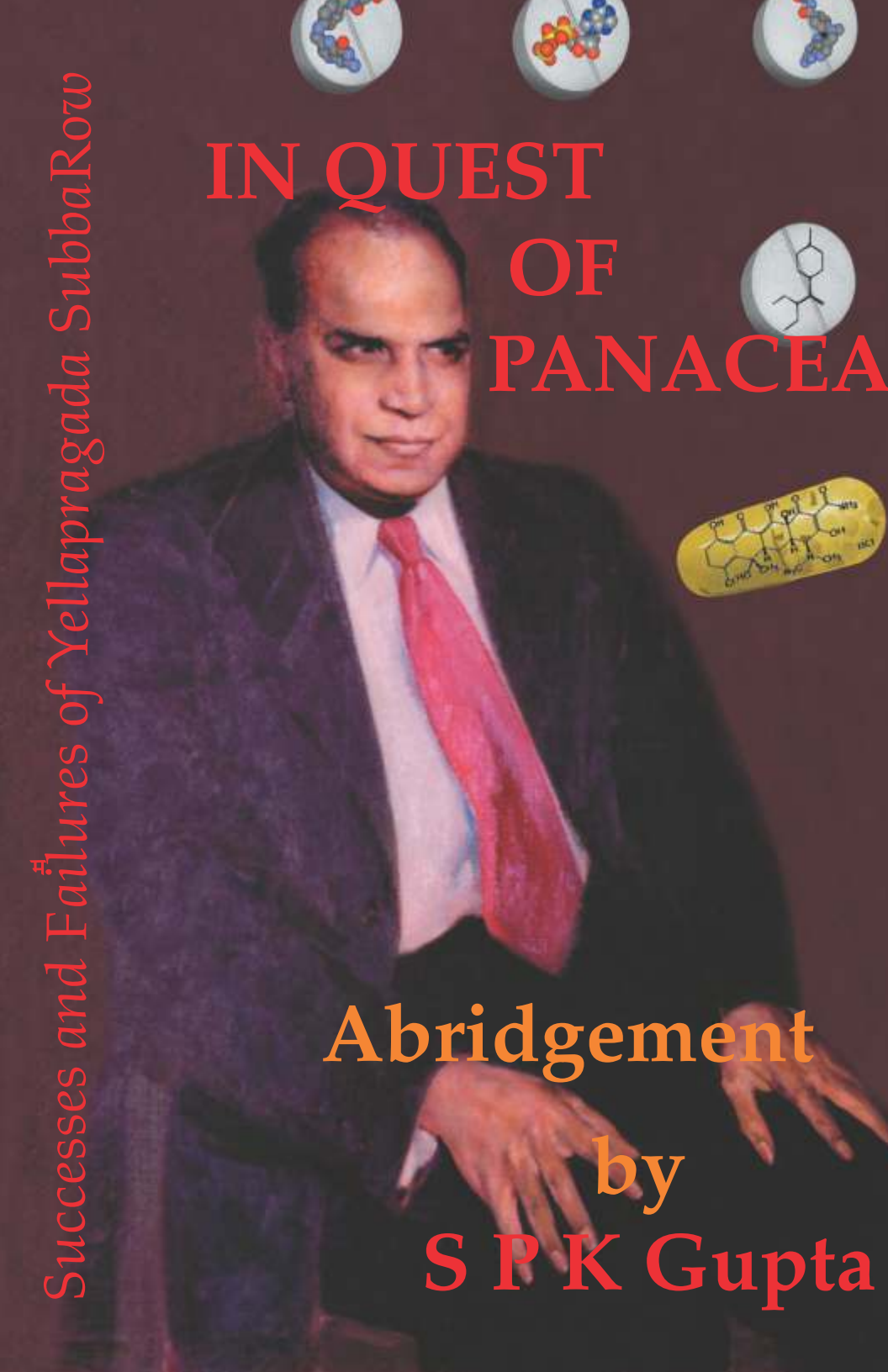
IN QUEST
OF
PANACEA
Successes and Failures of Yellapragada SubbaRow
Abridgement
by
S P K Gupta

# IN QUEST OF PANACEA

By

S P K GUPTA

in collaboration with

Dr. Edgar L. Milford

An Abridgement by the Author

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**William Parker**

## By the Same Author

Apostle John and Gandhi (**Navajivan**)

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A Wreath for Doctor Ramayya,

By Ghen Shangin Berezovsky

Translatied from Russian with Achala Jain (Evelyn)

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IN QUEST OF PANACEA

***Successes and Failures of Yellapragada SubbaRow***

***written in collaboration with Dr Edgar L Milford (Evelyn)***

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Collaborator: Dr Edgar Louis. Milford (1895-1999) was a Haitian- born and -educated American allergist and archivist with Lederle Laboratories.

# FOREWORD

by

Pushpa Mitra Bhargava PhD

**Yellapragada SubbaRow (1895-1948)**

# He Transformed Science; Changed Lives

Most of the famous scientists around the world are known only for one major discovery that has had a lasting impact on our lives: Wilhelm Roentgen for x rays, Marie Curie for radium, C V Raman for the scattering of light by liquids, P M S Blackett for cosmic rays, Ronald Ross for the life cycle of the malarial parasite, Alexander Fleming for penicillin—all awarded the Nobel Prize for their one major discovery.

There have been a few scientists known for two discoveries: Albert Einstein for the photoelectric effect and the theory of relativity, John Bardeen for transistors and superconductivity, Hargobind Khurana for the genetic code and synthesis of gene.

Occasionally a scientist makes a large number of discoveries albeit in only one field like Robert Woodward in organic chemistry.

Then there are persons who have made important contributions but have not received the Nobel Prize or equivalent honours like Jonas Salk who made the first polio vaccine, Michael Heidelberger the father of modern

immunology, G N. Ramachandran who discovered the structure of collagen the most abundant protein in our body and also laid the foundations for CT scan and NMR technologies.

Rarely, extremely rarely, a person comes on the world scene and transforms science and our lives by making a large number of major discoveries in — and otherwise makes important contributions to — more than one basic field and does not only not get a Nobel Prize but does not get to be known by name to most people, including scientists around the world.

I am referring to Yellapragada SubbaRow. Such an individual is perhaps born once in a thousand years or more. I do not believe there is any other person in the documented history of biology and medicine over the last 5000 years who made such a large number of basic discoveries that are applied so widely.

SubbaRow was born in India in 1895 and he died in USA in 1948 at the young age of 53.

He went to the United States in 1923 after graduating from the Madras Medical College and worked at Harvard Medical School until 1940 when he went to Lederle Laboratories to direct its medical research.

The search he directed at Lederle Laboratories for antibiotics with wider range of cures than the then available penicillin and streptomycin led to the discovery of polymyxin widely used even today in cattle-feed and Aureomycin the first of tetracycline antibiotics which all of us have had some time or the other in our lives. Tetracyclines have saved millions of lives over the last 50 years.

Aureomycin was presented to medicine in 1948 the year SubbaRow died. It was the first broad-spectrum antibiotic, that is, one effective against both gram-positive and gram-negative germs. It was thus more powerful than either Fleming's penicillin or Waksman's streptomycin.

When SubbaRow's centenary year began in 1994, tetracyclines —especially Doxycycline — helped confine and then eradicate the plague epidemic that broke out in Gujarat and Maharashtra. It was a debt SubbaRow paid to his motherland almost half a century after death which claimed him soon after the unveiling of Aureomycin before a medical gathering at the New York Academy of Sciences.

SubbaRow and his team of organic and biological chemists isolated folic acid from liver and a microbial source and then synthesized it in 1945.

By the clinical trials he organised, SubbaRow had the satisfaction of knowing that it cures tropical sprue which took him to the death's door while a medical student in Chennai and carried away two of his brothers.

It is a pity SubbaRow is not given the credit for laying the foundations for the isolation of Vitamin $B_{12}$ the anti-pernicious anaemia factor. Our daily requirement of $B_{12}$ is just one microgram. That is all you require but it is extremely important you get it. If you have those indescribable pains all over, chances are that you need it. SubbaRow spent years trying to isolate it from liver and succeeded but failed to recognise it. Others opened the door he found.

In 1965 or 1966, I met Sir Alexander Haddow, a very distinguished and handsome scientist then the director of the Chester Beatty Cancer Research Institute in London. We started talking about methotrexate which was being used widely not for curing but alleviating the suffering from Burkitt's lymphoma, one kind of cancer, and he said, 'Do you know that methotrexate was discovered by an

Indian?' You can imagine the sense of pride I felt.

SubbaRow got aminopterin, which reverses the action of folic acid, synthesised when reports of a clinical collaborator indicated that chemicals resembling the vitamin arrest the growth of cancer cells. He thus initiated the chemotherapeutic approach to the treatment of cancer. Methotrexate, a derivative of aminopterin, has since then been the drug of choice in childhood leukaemia and many adult cancers.

As Director of Research at Lederle, SubbaRow established a project for protecting American soldiers fighting in the Pacific from malaria and filariasis. He found in Hetrazan the cure for filariasis. It is today the most widely used drug against filariasis which leads to the deformity-causing elephantiasis.

Let me go backwards in time. When I raise my hand I am consuming energy. We derive energy from the food we take. A good part of what we eat is converted by the body into glucose. A mechanism in the body metabolises glucose and in the process generates energy the muscles use for running, raising hands and doing the work of everyday life. That alone wouldn't be enough. There must be ways of storing the energy obtained from food because

we are not eating food all the time. There was a hunt therefore in the 1920s for the chemical substances in the body acting as energy stores on which the body draws whenever it needs energy.

It was SubbaRow who co-discovered while working with Cyrus Fiske at Harvard the two chemicals - phosphocreatine and adenosine triphosphate - that store energy in our body. In fact all living organisms store phosphocreatine as their source of energy. When the body needs energy, ATP is converted into ADP (adenosine diphosphate) and ATP is replenished by phosphocreatine while the body rests.

Not only did he show how important phosphorus is for our body, SubbaRow also devised the perfect way of estimating phosphorus in living organism. There may not be any biologist of any kind anywhere in the world who has not some time or the other used the Fiske-SubbaRow Method of estimating phosphorus. In all fairness it should have been called the SubbaRow-Fiske method but SubbaRow put the name of his supervisor first on the paper describing it,

Trained first as a mathematician and physicist and then as a chemist with no formal training in biology, I got introduced to experimental biology through estimating phosphorus. And I used the Fiske-SubbaRow Method. That was in 1953. Hailing from Andhra as I did, I remember asking how he spelt his name Row and not Rao. As I learnt later he would have been the last man ever to cause a row!

If you look at citations of scientific papers - which is the way others use your scientific work and quote it in their publications - SubbaRow turns out to be one of the most highly cited scientists in the entire history of science.

Thus far about his work. What about the man himself? I have a wish list of ten persons from the beginning of human history I would have liked to meet personally. In it figures SubbaRow along with Chanakya, Ashoka, Leonardo da Vinci. I regret I never knew him. My first visit to USA was five years after he died but I have met and talked about SubbaRow with people who knew him intimately.

What came through in these talks, apart from his scientific brilliance, was his tremendous modesty and self-effacement. This was very difficult to understand as he was driven by a desire to be famous. But he was at the same time generous in giving credit for what he had done to someone who stood to gain a great deal thereby. It is difficult to reconcile these two qualities but all of us have a little bit of such contradictions in us.

Fiske would not have got the position he did at Harvard but for SubbaRow sharing with him the credit for the method of estimating phosphorus in biological fluids. My friend, S P K Gupta, in his biography of SubbaRow has documented many such acts of his to get a friend or a colleague a promotion or a job or an advantage.

SubbaRow's cultural pluralism is another thing that comes through in his documented life and work and in personal dialogues with people who knew him. He had this multiplicity of backgrounds which intermeshed in his

personality: He was extremely Indian and identified himself as an Indian. He was conversant with our ancient scriptures and his early work was in Ayurveda. But he also provided financial support to the Church, especially to churches which seemed to have a universal element in their beliefs and to their education programmes. It is strange that while he was an Indian in reality always, an Indian visiting him in USA told his family in India that SubbaRow had become totally Americanised. Appearances can be deceptive!

We must give credit to the United States for giving him the kinds of facilities to work not previously given to any Indian. But there is another side to the story that must be told. Let me quote from the biography, *In Quest of Panacea*, some bits that show how politics operate in the world:

"SubbaRow's admission to the U.S. and his stay there for a quarter of a century was possible because he went there as 'a physician' and qualified himself as a 'chemist' two of the professions that were exempt from the ban on immigration of Indians in force from 1917."

The Supreme Court ruled that Hindus were not Caucasians and the President excluded from American citizenship even those Indians who had been legal immigrants and had met the minimum residence requirement.

"Although he could get his 'student' visa, originally valid

for two years, periodically extended because he belonged to the excepted category, 'he was always mortally afraid . . . that he might be picked up for some minor infraction of the law and be shipped back to India . . . Then came the Second World War and the Alien Registration Act of 1940. SubbaRow had always to carry from then on a card bearing his right thumb impression, signature and registered number (3420564) testifying to his status as an 'alien', one of the 3896 East Indians on the Registry. And he had to report his address every three months to the Department of Justice in Washington.

"In 1942, he had to get special clearance because his position as Director of Research at Lederle was considered sensitive in view of his supervision of the processing of blood albumin for supply to the Navy and of the research on tetanus and gas gangrene toxoid that was of interest to the Army and the Navy. The clearance was given after a declaration by his company that it 'never had any reason to doubt his devotion and allegiance to the United States' and a thorough investigation was made of his record both at Boston and at Pearl River."

*The New Republic* fulminated in 1943 against the notion that natives of India like SubbaRow and other world-

renowned scientists then playing valuable roles in USA in helping to win the War were unfit for American citizenship that was 'freely granted to the most backward and ignorant Balkan peasant'. That year a number of bills were introduced in the Senate and the House of Representatives for lifting the citizenship bar on Indians. One of them reached the statute book in July 1946.

SubbaRow wished to shed the stigma of being an 'alien' amidst people with whom he had lived 25 years and had thrown his lot, but it took a year for him to get the ruling of the Immigration and Naturalization Service that he had been admitted legally into the United States. He spread the good news among his associates but he did not in the next twelve months he lived file his 'Declaration of Intention' the necessary first step to get the American citizenship.

SubbaRow felt within he was an Indian and he died an Indian.

When he died on August 8, 1948, obituaries appeared in *Science*, New York *Times*, New York *Herald-Tribune* and newspapers and journals in many parts of the world. The *Herald-Tribune* called him 'one of the most eminent medical minds of the Century'.

Yellapragada SubbaRow was not born great; his mother had to sell the little jewellery she possessed to provide for his education. Nor was greatness thrust upon him. He achieved greatness by imagination, self-confidence, love of fellow humans and an inner compulsion to alleviate human suffering. And he did what no other Indian had ever done *till then* on foreign soil: he made some of the most important and seminal contributions that were destined to transform a whole range of basic and applied sciences and save innumerable human lives. If there were a Nobel Prize for those who died virtually unknown but whose accomplishments lit the path of many who came later, SubbaRow would surely be among the first to receive it.

Even today in our country very few people know of him. The efforts of the Centenary Committee succeeded in getting the government issue a stamp in his honour in 1995. But he has not been given the appropriate recognition by the nation till today. We have given the Bharat Ratna posthumously to others. Why not to Yellapragada SubbaRow?

# OVERTURE

# A Million Good Turns around the World

**YELLAPRAGADA SUBBAROW** was a man driven by an insatiable thirst for fame.

Mankind owes to this drive the conquest of many illnesses that have plagued it for ages, the understanding of such life processes as muscular contraction which gets the living world's work done.

And yet mankind knows him little. "You've probably never heard of Dr. Yellapragada SubbaRow", an American author told his magazine readers after SubbaRow's death. "Yet because he lived you may be alive and well today. Because he lived you may live longer".

Five decades have since passed, half of a century of continued protection to people everywhere by the drugs developed by a scientist who has remained little known.

How in spite of such achievements can a scientist, especially a scientist who thirsted for fame, remain obscure in this age of instant communication?

SubbaRow was “a poor businessman” is the answer of a patent attorney who, after going through his laboratory records, is convinced of his genius as a chemist and is astonished he had not taken any of the steps that scientists everywhere consider routine for linking their name to their handiwork.

He was invariably in the audience when a colleague or a collaborator, pushed by him to the limelight, took the bow as each fruit of research directed by SubbaRow was revealed to the public.

He never granted interviews to the press. He never made the rounds of the academics which apportion accolades among the achievers. He never went on lecture tours. He never did any of these and other things required of anyone with the least pretension to awards, honours and recognition and without which one cannot achieve glory. How then was he a glory hunter’? And what was the kind of fame he was after?

SubbaRow was only thirteen when he ran away from his poverty-stricken home, persuading a cousin to accompany him, saying wealth and fame awaited them in Varanasi. He had a formula for making millions by selling bananas to pilgrims who flock to the Holy City

from all over India.

Intercepted and brought back by men sent in pursuit by his mother and pushed by her determinedly to scholastic achievements, he did well in mathematical studies and could well have won distinction as a wizard in mathematics.

But he drifted in another direction. It seemed to him that politics, medicine, high finance and even humanitarianism as avenues to fame were all *maya*, mere illusion. Even good works were to be spurned as they brought rewards in kind. He would join the Ramakrishna Mission and become a *sanyasin*.

Since he could not be admitted into the monastic order without the permission of his mother who was keen on worldly successes for him, the Mission which believed in good works persuaded him to enter the medical college so that he could serve in its clinics as a doctor. SubbaRow regarded the step as a means to enter the Ramakrishna Mission by the backdoor. His mother was puzzled by his apparently whimsical switch of interest from mathematics to medicine but was reassured when he told her: “I must win a name in the world. Then only would life be worthwhile. If it comes to that, one must

even be prepared to do something evil and win fame". As if to prove he could be cold blooded when it came to removing obstacles to his goal, he married a rich girl to finance his medical education although he knew marriage and family life were not meant for him.

His medical studies raised serious misgivings about the soundness of the basic tenets of his other worldly philosophy and he decided his life's work lay in unravelling the mysteries not of man's relation-ship to God but of man's responsibility to his fellow men.

The new goal would have permitted him to win fame by devoting his life to the treatment of the sick without expectations of financial reward, but his years in medical college convinced him that modern medicine was then powerless against many diseases.

He took up a position therefore in the Madras Ayurvedic College in the hope that he could wrest potent drugs from Ayurveda which had rescued him from the jaws of death a few years earlier when modern medicine had failed him. He quickly rose to be Vice Principal of the college and within his grasp was, it seemed, the principal-ship and glory that would go with it as a new synthesizer of the modern and ancient

arts of healing the sick.

He was not fooled however, nor did he wish to fool the world. The Ayurvedic College was not the place for any sustained medical research.

So with a determination that bordered on the unscrupulous, he planned once again his escape from home. This time, he succeeded. He rallied sponsors for his trip to the United States by leading them to believe he had secured an opportunity to win a place in Western medicine for the theory and practice of Ayurveda. He enrolled him-self in an American college for a course in Western medicine on the strength of a scholarship tenable only for non medical studies. He left with his wife's consent after promising an early return, a pro-mise he could not fulfil.

He did his duty by the professor who took him into the Harvard School of Tropical Medicine by earning a diploma at the price of a year of extreme personal privation. The Diploma was of no use to him as he never intended to use it for hanging out a doctor's shingle. But he used his foothold in Harvard to get enrolled in the "non medical" biochemistry course of the Medical School by the time the first instalment of his Indian

scholarship was paid out by the administering trust: by tarrying, the trustees saved him from violating the conditions of the scholarship.

He made a spectacular start in biochemical studies he took up in the summer of 1924. Before the year was out, the American Society of Biological Chemists set its seal of approval on a valuable laboratory tool he devised which is used to this date by biochemists the world over: “a rapid colorimetric method” for estimation of phosphorus in body fluids and tissues.

However, this did not bring instant fame to our biochemical prodigy. He had worked out the method under the supervision of Dr. Cyrus Fiske and courtesy in research required that it bore the names of both men. Moreover, association with a professor well established in the field would make the method more readily accept-able to the profession.

So it was as “the Fiske SubbaRow Method” that it was presented in the biochemistry textbooks that came out in 1925. He wrote home about all this but strictly forbade his people from talking of it to anybody. “Publicity is bad,” he enjoined on his father in law. He sent reprints for the scholarship board but insisted:

“Please do not advertise.” How does one build fame for oneself with self abnegation and avoidance of publicity, he never paused to consider.

A follow up study on the phosphorus method appeared to give him and Fiske a glimpse into the fate of sugar in blood after the ad-ministration of insulin. He thought the stars had chosen them to solve a problem that had baffled many Nobel prize winning biochemists including Banting, the discoverer of insulin therapy for diabetes. It was a mirage, but the trail nevertheless led to “the greatest discovery” in twenty years of a world wide study of phosphorus metabolism a discovery that showed the Nobel Committee erred in awarding the 1922 prize in medicine and physiology to Archibald Hill and Otto Meyerhof for explaining muscular contraction in terms of the conversion of glycogen to lactic acid.

Phosphocreatine and adenosine triphosphate (ATP) discovered by SubbaRow in Fiske’s laboratory proved to be *the* sources of muscular energy which make possible all physical activities of living beings.

SubbaRow wrote home: “I have risen up in fame and my name is known in every biochemistry department

in the world." But only the latter half of the statement was true. The slowness of the biochemical orthodoxy in accepting new ideas, the natural reluctance of the prestigious Nobel Committee to admit it had awarded a prize rather prematurely and controversies over publication priorities cheated Fiske and SubbaRow of full credit for what is undoubtedly a key discovery in the understanding of the riddle of life itself.

There was general recognition among Harvard Medical School faculty and staff that to all these successive discoveries in Fiske's laboratory SubbaRow had made increasingly independent contributions, that the discoveries were the result mostly of the younger collaborator's work.

But SubbaRow unhesitatingly renounced personal credit when Fiske's promotion as head of the department of biochemistry hung in the balance in 1935. He told Harvard authorities that his own contributions were mostly technical and that the "brains behind the work as well as the finer side of the technique" were all entirely Fiske's.

SubbaRow had by then a new passion and the discoveries in muscle chemistry were for him entirely

a matter of past record. He had just achieved a breakthrough in the concentration of the substance in liver that helped pernicious anaemia patients. He was entirely preoccupied with the isolation of this cure for a deficiency disease then believed to be closely related to tropical sprue which had afflicted all the Yellapragada brothers and taken the life of one.

The sacrifice however broke a ground rule any aspirant for fame has necessarily to observe: consolidate reputation gained from one achievement before taking on a new challenge.

Worse, it severely handicapped his hunt for vitamins in liver. Harvard authorities saw no reason to promote from his lowly staff position one who, on his own admission, had been no more than a pair of extra hands for Fiske. Denied qualified assistants, laboratory facilities and budgets that would have gone with a faculty appointment that was his due, SubbaRow had to depend on outside help over which he had but a modicum of control for man power and material assistance, analytical work and clinical collaboration. His better endowed rivals won glory as discoverers of the vitamin properties of nicotinic acid and pantothenic

acid. And the final step in the isolation of vitamin $B_{12}$ eluded him.

SubbaRow again left home, left Harvard which had not been a bounteous mother but a foster mother (Alma Mater). It trained and sheltered him for over a decade but failed to appreciate him and provide a place for his life's work.

He left for Lederle Laboratories at Pearl River, New York State, which wanted him to direct a new research facility it would build for him. Lederle had a profitable business with liver preparations based on technical know how acquired from him in return for liver supplies and large scale isolation facilities on weekends. Lederle had turned to him in an effort to secure a place in the new field of vitamins and antibiotics which were rendering its main line of vaccines, sera and tonics obsolete. This was his chance to provide modem medicine with an arsenal of potent drugs to fight disease.

In his new laboratories nestled in picturesque Rockland County, he gathered a group of young men fresh out of university graduate schools and some veteran science specialists and technicians.

He was the maestro, orchestrating the brilliant new ideas of the young in the most creative years of their life and a new creativity induced in veterans by assigning them tasks in which they had no previous experience.

He was the MD for the PhDs, motivating them with his dedication to the task of alleviating the ailments of humanity. He was the PhD who got the MDs to help him and his boys fashion chemicals to match the microbes.

He was a man of all sciences, a chemist among chemists, a parasitologist among parasitologists and a clinician among clinicians. He would go from laboratory to laboratory, pacing up and down with doctors and project leaders who had run into problems or were stuck on something and say, “Now you should do this and this and this.” And, amazingly enough, the work would go forward.

After an initial incubation period of five years, SubbaRow and his team of young scientists and “amateur” experts, in a fabulous three year period of great discoveries, presented to the medical world a vitamin that avenged the death of SubbaRow’s brother

from tropical sprue, an anti filarial that fought an old scourge of India and other tropical countries, anti vitamins which opened up a hopeful new line of attack on cancer, and an antibiotic that seemed like a panacea for many bacterial and some viral infections.

Here was the opportunity for the old aspirant for fame. He was in the Harvard tradition "the brain" and could perhaps have claimed that the boys he had guided and inspired were just so many "hands". But that would have been unfair to them as it would have been so unworthy of himself. "The victories of science are rarely won single handed," he insisted. "No one man should get the credit."

He perhaps had the greatest sentimental attachment to folic acid. He had led successive groups through isolation of this vitamin from liver, exploitation of a microbial broth which was a richer source and final chemical synthesis. And it turned out to be the cure for tropical sprue that had so nearly taken his life back in the Madras Medical College days. But when the boys discussed the authorship of the paper announcing folic acid synthesis, he was busy coordinating extensive clinical trials in far flung places to prove, in the face of

prejudice in the medical establishment, its value in nutritional anaemias. They decided to include him in the alphabetical list of the sixteen workers who had contributed to the synthesis and went to him for his signature. SubbaRow regarded it a compliment which he returned by choosing the university professor under whom many of his folic acid scientists had trained to preside at the conference where the vitamin was formally presented to the medical world.

Such submersion of individual credit for contributions made to collective team achievements appears only fair. For there is no single phase of modern medical research that can be considered the key to ultimate success. There is no single criterion for awarding the accolade. A promising drug has to cross many hurdles: initial production of the chemical either in the test tube or in the fermentation broth of a mould, screening in animals first for activity and then for safety, large scale production and, finally, clinical trials. But mankind is not ready yet for the cult of the collective: it sees no glamour in a team and looks for symbols and most often the choice falls on the leader of the team.

SubbaRow, looking all the time for new drugs to

conquer disease, does not seem to have paused to realise that he could be the symbol of achievements by the research teams he was directing in such masterly fashion, organising them, motivating them and helping them cross hurdles each time they were held up. But he did regret having gone outside his team to seek a symbolic person for the folic acid achievement. Coy Waller, the youngest member of his folic team, had in his opinion made the most outstanding contribution. So when "Waller's shot gun synthesis" was adapted to produce a folic acid analogue that made a new approach to cancer therapy possible, he got young Waller to present it to the medical world and receive the acclaim. His enthusiasm for brilliant members of his research teams was now so unbounded that he began to push into the limelight those whose dedication most nearly matched his own:

- Redginal Hewitt noticed the anti-filarial activity of a chemical among the scores sent to him for routine screening in rats and provided thereby the lead for synthesis of Hetrazan.
- Sydney Farber, while treating leukaemia patients, switched from folic acid *conjugates* to folic acid

*antagonists* and blazed the trail since followed by cancer fighters all over the world.

- Benjamin Duggar screened thousands of moulds and supplied SubbaRow with hundreds of microbe killers one of which yielded Aureomycin, the world's first tetracycline antibiotic.

While Duggar as "discoverer" was presenting Aureomycin at the New York Academy of Sciences, SubbaRow was seen in the back row talking animatedly with an assistant about engineering plans for the new cancer research laboratory that would be built for him at a nearby town by his company.

SubbaRow died two weeks later, a stranger to Lady Fame whom he had pursued all his life but to whom he never presented his suit. His last expressed wish to colleagues was: "If God will spare me another couple of years, may be we can cure another disease."

The Karolinska Institutet in Stockholm which awards the Nobel Prize in physiology and medicine used to have a portrait of SubbaRow, and SubbaRow's colleagues who saw it in the 50's speculated whether he was ever considered for the Prize which so fascinated him during his early years at Harvard.

J. Erik Jorpes, professor emeritus of medical chemistry at the Institutet and SubbaRow's contemporary as a research scientist in the vitamin and hormone field, is most discreet in discussing the question but says: "For Doctor SubbaRow I had a real admiration . . . When I started to collect photographs of men who have made real contributions to medical chemistry, SubbaRow was one of my first candidates."

The real point is that SubbaRow never presented himself as a candidate for any honour.

Poli Kittu, amateur Boy Scout in the Kannada play of the same name, was ever in quest of the daily good turn that would win re-cognition for him from the team. But he never realized that his spontaneous acts of aid and assistance to fellow humans were far worthier than those reported to the scout master by his peers.

SubbaRow too never recognised any of his many contributions to the understanding of life processes and to the conquest of disease as worthy of the fame he thirsted for. A medical warrior's quest never ends so long as there is a single illness that remains to be conquered.

SubbaRow is not famous, although there is now an

increasing awareness that folic acid, tetracyclines, methotrexate and diethylcarbamazine came out of the research he led and directed, but his gifts to biochemistry and medicine keep performing a million good turns for mankind each day around the world.

# IN QUEST OF PANACEA

# Mendicant or Doctor of Medicine

Venkamma was worried. It was already one past noon. Her son, SubbaRow, and nephew, Venkataramayya, were still not back from school. Satyanarayana, her youngest son, sensed her anxiety as she paced up and down. He told her that they had carried a pack of clothing when they left home at the usual school going hour of seven in the morning. And he had got a beating from Venkataramayya because he had asked the inauspicious question, “Where are you going?”

Venkamma got it in a flash. The boys had run away from home. SubbaRow had timed the escapade well. Jagannadham, his father, was away in Vijayanagaram, on another attempt to get a job after illness had forced him to retire from his job as head clerk in the taluka office at Narasapuram in West Godavari district of what is now Andhra Pradesh.

She lost no time. She rushed to the cart stand and met the cart man who had just returned to Narasapuram after leaving the boys at Palakol. She took the same cart along with a classmate of the boys to Palakol. At the Palakol cart stand they met the man who said he had left two boys at the river harbour in Maruteru.

Venkamma asked the cart man to turn back and take her, the classmate and the Narasapuram cart man. They learnt at Maruteru that the boys had already left by the boat for Nidadavolu. Venkamma sent the classmate on a bicycle with one Somanna to intercept the boat before it reached the railhead.

The year was 1908. The boats on the Narasapuram--Nidadavolu canal were, as they still are, pulled with ropes by men trudging along the bank.

The bicycle riders caught up with the boat when it was only two miles from Nidadavolu. They persuaded the boat pullers to tie the rope to a road side tree and boarded the boat.

The boys were hauled into a boat going the other way. SubbaRow tried to kill himself by jumping into the canal and had to be kept pinned to the floor of the boat. It was two in the morning when the boat reached Maruteru. Venkamma was pacing up and down the bank. She caught SubbaRow by the forelock, dragged him out to the bank and gave him a good beating.

It was Venkataramayya who broke down and came out with the story. They were on their way to Kasi. SubbaRow had persuaded his cousin to go along with

a plan to make lakhs by selling bananas to pilgrims while eating free at a different *dharmashala* each day. For SubbaRow it was to be an escape from family poverty and Venkamma's domineering passion to get him educated at any cost. Venkataramayya's was a relatively rich family which had entrusted his education to the care of Venkamma. He had fallen in line with the plan only because he did not wish to be separated from

SubbaRow for whom he had developed a close attachment during the four months since he came under

Venkamma's guardianship. They had left with the monthly remittance of Rs. 60 Venkataramayya had just received from his father.

S U B B A R O W belonged to the third generation of a Niyogi Brahmin family, which was trying to make the transition to the modern times with the help of education.

His grandfather, Yellapragada Subba Raju, a descendant of Yellanna who was *preggada* or minister in the court of Tanisha, the illustrious seventeenth century Nawab of Golconda.

Yellapragadas or descendants of Yellanna the preggada had been *karnams* (revenue accountants) of Kotturu Jagannadhaparam, three miles east of Mukteswaram on River Godavari for two centuries. Subba Raju found the declining income from the lands, which went with the *karnam* job not sufficient to support the joint family.

He handed over the job and the ancestral lands to his brother and moved with his wife to a town where their two children could get modern schooling. The elder son died young but the second, Jagannadham, passed the high school examination and entered the revenue service of the then Madras provincial government.

Jagannadham was revenue inspector at Yendagandi when he married Venkamma, the younger sister of his first wife, who died leaving no issue behind. SubbaRow was the fourth of the seven children of this marriage. He was born on January 12, 1895 in Bhimavaram in West Godavari district in a house just across the street from the taluka office where Jagannadham was head clerk. He was a bonny and chubby baby. However, he did not learn to walk until a day in his fourth year when he took his first steps while trying to reach out for the low hanging white bolls of a cotton plant in the backyard of the house.

He was fond of his sister, Annapurna, and the first school he attended was a girls' school in Narasapuram where she studied after Jagannadham's transfer there. When he -passed the primer examination, he was enrolled at the Taylor High School, a boys' institution.

But he continued to play with his sister and her companions and learnt to render fairly well the favourite songs of the womenfolk. He retained all his life love and affection for Annapurna. Annapurna was not the only woman in his life who won his loyalty through the sisterly approach. But SubbaRow did not like domineering women.

He did poorly at school because of his resentment at the authoritarian way Venkamma tried to educate her children. He would run away from school and would be traced in the woods outside the town. He was once struck off the rolls of the Taylor High School. He was readmitted but his heart was not in studies. He appeared to be out of his element at school like a fast ocean liner stuck in a river, and made his impatient attempt to escape to Kasi Varanasi.

It is hard to blame Venkamma. The responsibility to bring up and educate the children had fallen on her as Jagannadham remained sick after taking an early retirement on a meagre pension. Her boys owed everything in their life to her grit and determination in the face of poverty during their years of upbringing.

SubbaRow attended school regularly after Venkamma

foiled his attempt to run away from home and school. He was softened by new family misfortunes. Jagannadham returned from Vijayanagaram as he could get no job there and fell sick with beriberi. They had to move to Modekurru and live with Balamma, widowed sister of Venkamma.

SubbaRow did well in mathematics but could work up no interest in other subjects. He somehow passed the class examinations but failed in July 1914 to pass the matriculation examination in his first attempt.

He was sent to his elder brother Purushottam at Rajahmundry to study at the Viresalingam Theistic High School there. He admired Purushottam who had been rusticated from college for his part in the "Vandemataram Movement" against the partition of Bengal, had gone all the way to Allahabad to secure his M.A. and Ll.B. degrees and had accepted a poorly paid teacher's job at the VTH School.

Purushottam was a good influence on SubbaRow. -A greater influence was Chilakamarti Lakshminarasimham, a poet, who inculcated in SubbaRow some of Kandukuri Veeresalingam's zeal for a Hindu religion shorn of its ritual, superstition and

orthodoxy. Veeresalingam himself was there at the School he had set up to try out new ideas in education. It all made a deep impression on SubbaRow. But his involvement in the intellectual ferment of the city left him no time or taste for studies.

SubbaRow fared badly again in the matriculation examination. He was sent the next year at great family sacrifice to Madras City to study at the Hindu High School in Triplicane and make his third attempt at matriculation.

He rushed home in January 1915 when his father died. Venkamma sold the last of her gold ornaments on the fifteenth day of Jagannadham's death to provide SubbaRow his train fare back to Madras and money for the remaining two months before the examinations.

He passed the examination this time and entered the Presidency College in Madras opting for Mathematics, Physics and Chemistry besides English and Telugu for the Intermediate course.

But the study of these subjects seemed to him less important than the fixing of his goals in life. What did he want to get out of life and to what end should he devote his life? Freedom of his people, the treatment of

the sick, acquisition of the highest knowledge to share with the less learned? But should he not give a thought for himself? How about making millions like Henry Ford? But one has to struggle a lifetime to achieve any of these goals. Why not just marry a nice girl, have no children and lead a peaceful, contented life?

SubbaRow knew what each of these goals meant. The chosen goal must be one that would satisfy all his important desires. "One will become a wreck," he wrote later, "if one loves women and wants to become a monk just to achieve fame. It is impossible to desire a peaceful life and yet hope to acquire great riches."

He rejected in the end every one of the goals he put before himself: politics, medicine and high finance as well as happy matrimony. The underlying motive in each of these — career, patriotism, humanitarianism, wealth-power and unmixed happiness — was born of *maya*, mere illusion. He would turn his back on the world and its illusions. He would become a sanyasin and spend the rest of his life seeking in religion the knowledge about the relation of man to God.

SubbaRow had been convinced by his father in his quiet way that the only lasting good lies in spiritual values.

He had listened each evening while Jagannadham in Modekurru read from the Telugu versions of Ramayana and Mahabharata. His Imagination was caught by the spiritual discussions in these epics as they narrated the heroic deeds of the ancient kings.

He took care to see that his mother did not know that he had applied at the Ramakrishna Ashram. He walked three miles every morning and evening for two years from Triplicane to the Ashram on Brodie's Road to study Upanishads and Bhagavad Gita, Bible and Koran. He also practised yoga exercises and became proficient in astrology.

SubbaRow naturally neglected his classes. But he studied in the hostel because of the fear that his kindly roommate, B Narayanamurty, would otherwise end the arrangement which largely supported him in Madras. And he passed the Intermediate examination with distinction in Mathematics.

His professors asked him to take the honours course in mathematics but he applied at the Madras Medical College as advised by the *swamins* of the Ramakrishna Mission. He could serve in one of the clinics run by the Mission, the swamins thought. SubbaRow believed his

case for acceptance into the Ramakrishna Order would be strengthened if he acted according to their advice.

He told Venkamma puzzled by his "whim of the last moment": "Without money, we can do nothing good for anyone. As a doctor, I will at least be able to save a few patients from their suffering. I must make my name in the world." She was pleased by these words of worldly wisdom, but he continued to neglect classes during his first two years at the Medical College. He got deeper and deeper into the study of Sankaracharya's Adwaita philosophy. At the end of the two years, he found himself unable to accept two of the basic tenets of Sankaracharya. His medical studies challenged Sankara's view that world is there only because there are beings with sense organs to perceive it., Nor could he agree to give "good works" only secondary importance like Sankara who argued that they bring rewards and prevent the individual soul from achieving emancipation by losing its identity in the Divine Self. SubbaRow believed in "good works" and he had put his faith in Adwaita to help him find a goal in life.

He deliberated over his disillusionment with Adwaita for a month and decided he would give up his search

for knowledge about the relation of man to God. He would instead find out what is man's responsibility to his follow men. He began therefore in his third year at medical college to study hard.

But Narayanamurty could no more support him, and SubbaRow could not pay even for food. The proprietor of the hotel where he ate came in search of him and pleaded: "Do not stop eating at my hotel. You may pay when you can. It you cannot pay at all, just forget about it."

When there was no money to pay his term fee in June 1918, SubbaRow went to Kakinada to meet those from whom Venkamma had previously secured him aid. He was introduced to the Kastury family of Anaparthi. He was a bright young man in need of help to complete his education. The Kastury family had daughters to marry off. SubbaRow "saw" the girls but said marriage was not for penniless ones like him. Suryaprakasa Rao, head of the Kastury family, decided to support SubbaRow's education unconditionally. But friends of the family as well as Venkamma persuaded SubbaRow within six months to agree to marry Seshagiri, grand daughter of Suryaprakasa Rao. They agreed to his

condition that he would set up home with Seshagiri three years after he got his medical degree so that he might get advanced research training abroad.

Before the marriage could be celebrated, SubbaRow was bed ridden with severe diarrhoea. The best allopathic doctors in Madras city treated him but his condition worsened. Venkamma went to Dr. Achanta Lakshmi Pathi who held a degree in Western medicine but practised Ayurveda. Dr. Lakshmi Pathi diagnosed the diarrhoea as due to sprue, an illness caused by nutritional deficiency. SubbaRow began to rally with the fourth or the fifth done of simple drugs he administered. He gradually recovered with the help of fresh juices the doctor prescribed and was well within four weeks. He was intrigued by the simple, yet efficacious remedies of Ayurveda. He went to thank Dr. Lakshmi Pathi, said he wanted to learn more about Ayurveda and offered to serve his saviour after he graduated from the medical college.

The wedding of SubbaRow with Seshagiri took place at Anaparthi on May 10, 1919 daring the summer vacation after the third year medical examination. All his worries about funds to complete the medical college

were at an end,

When Gandhiji launched the Non Co Operation movement in August 1920, SubbaRow seriously considered withdrawing from college. He did not take the fateful stop only because it would make him "a miserable failure", a life wreck fit only for the lunatic asylum. But he accepted Gandhiji's call to boycott British made goods. He gave up the imported "1702 Mull" fashionable among medical students and took to handloom dhotis and *khaddar* shirts.

His surgical gowns made of khaddar incurred the displeasure of M. C. Bradfield, professor of surgery, who told him: "Wait until Gandhi becomes Viceroy." SubbaRow said: "Gandhiji will not condescend to be Viceroy." At the final medical examination, SubbaRow secured good marks in all papers except Surgery. He was awarded the lesser L.M.S. Certificate instead of the M.B.B.S. degree.

He had decided much earlier that he would not practise medicine but dedicate himself to research on medicines which doctors then so woefully lacked to fight many diseases.

Indians with such ambitions went those days to London

or Edinburgh but he was against studying in imperial Britain. The United States of America sounded like the right country to go when he met a young American doctor, John Fox Kendrick, who came to Madras to work on hookworm control in the tea estates of South India. Kendrick told him of Harvard School of Tropical Medicine and other American institutions working on research in tropical diseases. He also confirmed that his medical education in Madras would be recognised for admission into advanced medical courses in the U.S.A. SubbaRow applied to Harvard in May 1921 and received within a month a cablegram assuring admission into the university's courses in tropical medicine. His studies at Harvard were dependent on a scholarship from Malladi Satyalinga Naicker Charities

at Kakinada. His brother Purushottam, who could have persuaded the trustees to award him a scholarship, died at this time of tropical sprue. As he watched his brother shrink to a mere bag of bones and then die, a fierce resentment flared up in him. “Why is man so helpless against this wasting disease,” he asked himself. His determination to find drugs that cure such ailments was strengthened but the death of Purushottam meant there will be no Malladi scholarship in the immediate future. He returned to Madras and joined Dr. Lakshmi Pathi’s Madras Ayurvedic College as a lecturer in anatomy and physiology.

This college was one of the earliest attempts at putting Ayurveda on a modern footing. The ancients regarded Ayurveda as *punarnavam*, a science that renews itself in the light of experience, study and research. It was because *vaidyas* in medieval times had ignored this and relied superstitiously on the authority of old texts that Ayurveda is no match for Western medicine in the treatment of many diseases and in surgery.

The Madras Ayurvedic College was opened in 1912 by Deevi Gopalacharlu who came from a family of vaidyas of Machilipatnam. Gopalacharlu secured the services

of Dr. Lakshmi Pathi, just out of college with a degree in Western Medicine, to teach anatomy, physiology and midwifery at his college. When Gopalacharlu died in 1920, Lakshmi Pathi succeeded him as the principal of the college having in the meantime been trained in Ayurveda himself.

SubbaRow was an immediate success as a lecturer. The facility with which he referred students to particular paragraphs of specific passages in the textbooks awed the students. He had a way of making students understand all aspects of physiology easily. He was soon made Vice principal and entrusted with administrative duties as well because Dr. Lakshmi Pathi was appointed to the Madras Committee on the Indigenous Systems of Medicine.

He willingly performed his administrative duties in addition to the teaching chores. But it was in his study of Ayurveda that he found his greatest fulfilment during his eighteen months at the Ayurvedic College.

Western doctors those days believed that most, if not all diseases, were caused by germs (bacteria). A better understanding of bacteria and the mode of infection might help development of vaccines and sera for

prevention of illness, but what about treating a disease that has already secured a hold in human body, SubbaRow asked himself. With no sulpha drugs and antibiotics at that time, the helplessness of Western doctors in the face of most sicknesses was glaring.

And the bacterial theory of infection did not explain satisfactorily why persons exposed to the same germs in similar circumstances do not all fall sick. As he read the Ayurvedic texts, SubbaRow was impressed by the ancient Tridosha Theory which held that the human body and mind are governed by *kapha* the fluid matrix for the play of life, *pitta* the thermal mechanism which rules metabolic processes and *vata* the life principle which guides all activities of nerves and muscles. The harmonious working of these three *doshas* is health and the break down of the harmony sickness. The *doshas* are thrown off balance when climatic changes become too intense or weak or perverse and the reserve powers of the body cannot cope with them, when wrongful conduct affects the body or when enjoyment of sensual pleasures go beyond moderation or capacity of the individual. When the doshas are in a state of imbalance, they get spoiled by genetic or congenital defects or

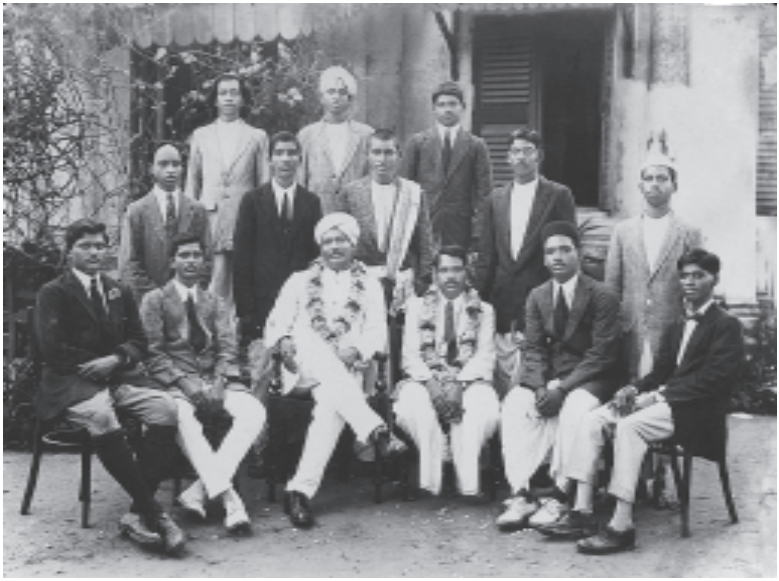
nutritional deficiencies, by physical, chemical and biological sources, or by disability caused by hunger, thirst, sleeplessness or fatigue.

If the doshas have been spoiled much and the person's constitution is weak, the disease takes an acute form and the body succumbs. If the vital powers of the body rally immediately, the spoiling process is reversed and the person survives. If the fighting forces are nearly of equal strength, a chronic illness follows and remissions and relapses take place until such time as the body or the disease gets sufficiently powerful to subdue the other.

The Tridosha Theory seemed to SubbaRow to make up for the inadequacies of Western theories. He wanted to test it. If animal experiments and treatment of the sick proved its validity, the Theory could be the basis for all further fights against disease. SubbaRow was struck by the similarity between the three doshas or humours and the hormones for which claims were being made in the West of miraculous transformation of imbeciles into normal children, rejuvenation of the impotent and cure of diabetics.

Dr. Charles Sajous, professor of endocrinology at the

University of Pennsylvania, was interested in what SubbaRow wrote to him about this, asked for details about the Tridosha Theory but did not encourage SubbaRow's ambition to do comparative research under his auspices in Philadelphia. Han Selye of the University of Montreal's Institute of Experimental Medicine and Surgery would a decade later propose



the "General Adaptation Syndrome" which explains onset of sickness in terms strikingly similar to the Tridosha Theory.

Along with his theoretical studies in Ayurveda,

SubbaRow initiated at the Madras Ayurvedic College clinical trials on modern lines of ayurvedic drugs for elephantiasis and other diseases. He published in the College journal an analysis of ayurvedic and allopathic literature on the diseases and asked *vaidyas* to try ayurvedic medicaments on their patients and communicate results to him. He also compiled with the help of students a 427 page manuscript on vegetable drugs described in the ancient ayurvedic texts. But he soon realised that Dr. Lakshmi Pathi's establishment was no place for sustained research. It just did not have the right atmosphere let alone equipment and facilities. But his settling down to the job at the College was opportunity for his mother and in laws to pressurise him to set up family with Seshagiri. He had to agree.

He also continued his efforts to get admission into Harvard School of Tropical Medicine. Dr. Richard Strong, Dean of the School, also turned down SubbaRow's request for opportunity to develop the Tridosha Theory and to standardise Indian herbal medicines "so that they will be useful for all systems of medicine". When SubbaRow agreed to give up his ambition, Strong said he will be admitted in the session

beginning September 1925.

SubbaRow consoled himself with the hope that "some other worthy person" would undertake the synthesis of the theories and practices of Ayurveda and allopathy. He would regard his brief preoccupation with the task "a step" in his life's work.

He now had to persuade Seshagiri to let him go. She had during the years immediately after marriage suffered from neighbours' gossip in Anaparthi that her husband was either a mad man or a sanyasin. And during their few months of family life in Madras, they got to know very little of each other because of his preoccupations at the Ayurvedic College, although a certain fondness had developed between the two that might well have grown into love.

SubbaRow asked Seshagiri how long were they to live on the monthly salary of Rs.100 that Dr. Lakshmi Pathi gave him. "There will be money for us when I return from America," he told her. She suggested their going together to USA but an astrologer said there was "no sea voyage" in her horoscope. She gave her "unwilling consent" when he promised to return within three years. He left the Ayurvedic College when it closed for the

summer vacation, declining Lakshmi Pathi's offer of a higher salary and eventual transfer to him of the college principalship.

SubbaRow's renewed application for a scholarship was granted by the Malladi Satyalinga Naicker Charities when Dwarampudy Rami Reddy, a powerful politician of Ramachandrapuram taluka, backed it. When Rami Reddy's wife was ailing, SubbaRow had arranged and supervised successful surgery for her at the hospital in Pithapuram. The Trustees of the Charities voted SubbaRow an annual scholarship of Rs.1600 for three years but could not immediately release the first year's grant. The Zamindar of Vegayampeta, after a searching examination of SubbaRow's objectives, promised a gift of Rs.1000 but wanted some time to make the payment. Kastury Suryanarayana Murty, father of Seshagiri, saved the situation by raising a loan of Rs.2500 to be repaid when the first year's scholarship and the gift materialised.

The steamer ticket to New York cost Rs.1500. The fare included a "head tax" of eight dollars for the American Immigration Fund. This was for paying the return trip of aliens refused admission on arrival in the United

States.

As he went through the customs at Bombay, an English officer sneered: “What do you want to get an American education for?” “I am going to come back and take your job,” SubbaRow replied. When the S.S. Kashgar sailed from Bombay at noon on September 29, 1925, SubbaRow’s thoughts were mainly of the unbearable sorrow he had caused for Seshagiri who would not see him ever again.

# A Mystery of Life - Solved

SubbaRow arrived in Boston, where the Harvard School of Tropical Medicine was located, on October 26 and was disappointed it did not snow that night.

He spent the night at a rooming house in Copley, the city's poor quarters, worrying how he was going to fare in that expensive city. He had a hundred dollars left with him and needed another fifty just to make up the tuition fee which had to be paid before he could register himself at the School.

Dr. Strong heard his sorry tale in the morning. As he talked to the young man who had come halfway round the world to study at his school. He was truly impressed. "I never before had encountered such a probing mind, such a conviction of destiny," he later recalled. He offered to lend SubbaRow some money to enable him to register and meet other, immediate expenses and did everything to mitigate his woes.

By then the few fellowships available for specially qualified students in tropical medicine had all been awarded. Nothing came of Strong's efforts to get funds

for SubbaRow from the Harvard Medical School scholarship committee.

SubbaRow's certificate from Madras Medical College was good for admission to the School of Tropical Medicine but not for even a temporary license from Massachusetts State Board of Medical Licensure to get a job in one of the Boston hospitals as a junior doctor. SubbaRow did get a job in the Peter Bent Brigham Hospital, but it was one of a night porter. The fully qualified medical doctor washed urinals and bedpans of patients for three hours each night in return for something to eat while on duty and $50 a month which took care of the rent for a basement room in a house within a hundred yards of the School.

Dr. Strong worried about the night work interfering with SubbaRow's studies and affecting his health. He tried but could not get him the post of a laboratory assistant in the Boston City Hospital. He thereupon rearranged SubbaRow's attendance at lectures to reduce the strain. He could do no more.

The trouble was that SubbaRow was a foreigner at a time when Americans did not appreciate foreigners. Although started in the 17th century for "the education

of the English and Indian youth", Harvard University had long since lost its initial sympathy for the people mistaken by Columbus for the inhabitants of India. It had become the finishing school for the most promising sons of the aristocratic families of New England.

Boston city, where American Revolution was sparked off one December day in 1775 by the appearance in the harbour of three ships bearing Indian tea, had by the 1920's shed its liberal traditions. It was passing then through the last phase of a losing battle by the people of English origin against the growing influence of the Irish who arrived in America after them. The appearance of a stranger, especially one with a different colour, caused in such an atmosphere suspicion if not hostility. The image then of India in Boston was of an "uncivilised country" that Britain was trying to uplift and good as a market for manufactured American goods. When SubbaRow tried to talk to a Bostonian about the philosophy of Indian sages, he was told that 99 per cent of Indians knew nothing of Vedanta but believed in 33 crore gods. The few who had heard of India know of Mahatma Gandhi also but considered him a politician in the ascetic garb, an anarchist under the cloak of non violence or an idealist whose views would never be accepted by his people. Indian admiration for America, which had brought SubbaRow to Boston, was all one

way. The poor job rating of Indians in America was the reason for SubbaRow's difficulties in the big city.

And yet SubbaRow found, besides great understanding and kindness from Strong, a gift of money left by an unknown person in an envelope under the door of his room during a particularly hungry period. Dr. Strong and the donor who later turned out to be a young doctor strengthened SubbaRow's faith in humanity. He always remembered their help with emotion and tried to follow their example. SubbaRow made the best use of his opportunity to study under Dr. Strong and other members of the School staff without wasting time on self pity.

He worked for four months on a research project for the cultivation of *Endamoeba coli,* a protozoan parasite in the human intestinal canal. He could not continue the work because he could not get fresh specimens of the parasite but was happy it had helped him learn how to proceed with research work.

Professor Robert 0. Ward, who gave a course in tropical climatology, had studied the monsoon in India. SubbaRow told him about a school teacher in Kakinada who predicted rain days and hot days on the basis of

planetary and lunar positions. The professor thought it worth investigating if moon and the planets influence weather in the same way moon affects the ocean tide. SubbaRow tried but could not get him the records of the Kakinada teacher.

SubbaRow passed in May 1924 the required examinations and was awarded in the following month the Diploma of the Harvard University School of Tropical Medicine. The Harvard DTH, earned with such high cost in suffering, would have helped him to make a name for himself if he had returned home and practised Medicine. But it was worthless to him in Boston. He lost even the lowly Brigham hospital job in the summer and had to move to an even smaller room. His father in law got at this time a part of the first year's scholarship grant from the MSN Charities. SubbaRow was now bound to honour the terms of the scholarship which barred its use for the study of "law and general medicine". He therefore enrolled himself in a summer course in biochemistry. He needed not only the fee for the course but money for food and room rent. He wrote to his father in law to ask the Charities to make an advance payment of the second year's scholarship. He

got no response. He could turn to no one in Boston as Strong had left for South America on an expedition. He was helped through that summer the most miserable in his life – by monthly remittance of $50 from a Mr. Watson of New York.

It was at the Harvard Medical School that SubbaRow enrolled himself for the "non medical" summer course in biochemistry. He thought biochemistry mostly with the "normal" chemical processes of the body. But HMS and other medical institutions have biochemistry departments because a study of variations in the metabolic processes during illness does help throw light on the nature of disease.

Any way, SubbaRow's first biochemical assignment in

the summer of 1924 did appear to be far from any fight against disease, an ambition he thought he had given up when he called on Professor Otto Folin, head of HMS Department of Biochemistry.

Professor Folin was directing the talents of all in his department to development of methods for analysing small quantities of blood, urine and tissue. He had himself contributed to a process which proved the value of colour comparison in analysis of small amounts of material. Colorimetry, as this procedure is called, is based on the chemical law that the colour intensity of a solution depends on the amount of the material dissolved in it: the darker the colour the greater the concentration of the substance.

One such method developed in the department was for estimation of phosphorus in tissues. It was however unsatisfactory in many ways, and Folin assigned SubbaRow to assist Cyrus Hartwell Fiske, associate professor, in removing the difficulties with the phosphorus method.

Fiske was, as researcher, meticulous to a fault and, as teacher, a hard taskmaster and difficult to please. He would set the problem for his assistants and offer them

guidance but left them mostly on their own. However, he personally wrote up their results. It was an advantage to start one's probation with Fiske. His way with assistants very well suited SubbaRow who desired to learn "how to approach a new subject, how to think of its various aspects, how to put it to experiment, how to draw the most careful conclusions and how to form a reasonable and plausible hypothesis."

The task that Fiske gave SubbaRow was to search for a chemical agent that would, in small concentrations, completely convert phosphorus in the prepared tissue into a blue substance within the shortest possible time. The agent should not be affected by other tissue substances or by trichloroacetic acid used for removing protein from the tissue and should not require prior digestion of phosphorus with sulphuric acid.

It was a challenge that held SubbaRow's interest right away. He would come into the laboratory at eight in the morning and work with only brief breaks for food till well past midnight. He thrived on this tough regimen and, at the end of the gruelling summer, wrote home: "My health is perfect. I weigh five pounds more than I did when I started from Anaparthi."

The first satisfactory agent that SubbaRow found gave some 20 per cent more colour than hydroquinone previously used in phosphorus estimation. But it required 30 minutes to produce the maximum colour. Fiske said the ideal agent would be one which did the job in just five minutes.

SubbaRow continued his search. An old sample of 1,2,6-amino-naphthol-sulphonic acid gave very encouraging results. A purified sample of this turned out to be 50 times more active than hydroquinone. It produced within a fraction of a minute more intense colour than hydroquinone did in 30 minutes. But it was a difficult chemical to prepare. Fortunately it had an equally good isomer that could be prepared and purified easily. This was 1,2,4-amino-naphthol sulphonic acid which differed only in the way the groups of atoms were arranged in the molecule. It could also be readily bought in the market as it was in demand from dyestuff makers who called it the 1,2,4-acid.

SubbaRow worked the next four months day and night to perfect the phosphorus estimation procedure to the satisfaction of Fiske. The 1,2,4 acid stood every test. It did not require any big change in the procedure for

preparing the analytical material for colorimetric estimation. It gave accurate readings even in the presence of ten times more colour inhibiting material than was permissible with hydroquinone.

The "rapid colorimetric method for the estimation of inorganic phosphorus, organic phosphorus, organic phosphates and lipoid phosphorus in blood and urine", SubbaRow recorded proudly, "is correct to 1/100,000th of a grain".

Midway through all this work, when the Harvard Medical School reopened in September, Folin ended SubbaRow's probation and accepted him as a regular post graduate student. He also got him the night assistant's job in the School library and submitted to the Faculty of Medicine an application by SubbaRow for a scholarship. Shortly thereafter came a letter saying MSN Charities had raised the scholarship for the year to Rs.2000. A remittance of Rs.1000 came with the promise that the balance would be sent soon. SubbaRow cleared all his debts. When the Faculty of Medicine awarded him the scholarship, he used the 500 dollars to make the down payment on a research microscope that came up for sale on the death of a Harvard

professor. The School fee remained unpaid until the second Charities remittance came in the first quarter of 1925.

Fiske and SubbaRow were invited by the American Society of Biological Chemists to demonstrate the new phosphorus method before its annual meeting on December 29, 1924. Folin promptly asked SubbaRow to a celebration dinner at his home and promised him a bigger fellowship the following year.

The phosphorus procedure was presented to the Society as “Fiske SubbaRow Method of Estimation of Phosphorus”. SubbaRow had worked under the supervision of Fiske. Besides, the association of a biochemist of Fiske’s reputation would help its ready acceptance by the profession. SubbaRow was after all a novice, unknown to the scientific world until then. The method is so accurate and suitable for analysis of all kinds of biological and clinical material that it was adopted immediately by biochemical laboratories all over the world. It is used to this day in common analytical practice in many fields of biochemistry. It is one of the first procedures biochemistry students everywhere learn.

The East European flavour of his name, which rhymes with Saburov, hid the fact that SubbaRow was an Indian. Generations of biochemistry students in India believed him to be a Slav scientist.

SubbaRow wrote home in detail about all his work on the phosphorus method to assure his people and the MSN Charities that he was not wasting his time in America. But he begged of them not to publicise his achievement. Since his caution about publicity grew with each new achievement, SubbaRow's fame as a scientist rests on this relatively modest accomplishment as an apprentice in biochemistry. His name appears in textbooks and journal articles to this day related only to the "Fiske SubbaRow Method".

One of the observations made while testing the phosphorus method seemed to provide a clue to the mystery, what happens to blood sugar when insulin is administered? Biochemists began investigating the problem when Frederick Banting

showed that injections of insulin, the pancreatic hormone, keeps blood sugar under control and keeps diabetics alive.

SubbaRow worked for 18 months on the problem, often dieting and starving along with animals used in experiments. Some of the experiments had to be carried out without interruption for 48 hours. The first results seemed to indicate a solution to the problem that had baffled many Nobel Laureates including Banting.

SubbaRow was excused from keeping regular School hours. He was given an independent two-room laboratory, exempted from payment of tuition fee and appointed a research fellow with an $800

stipend,

But the initial observations were finally shown to be neither significant nor unique and the project had to be scrapped in September 1926.

Out of the ashes of this project however arose another project that provided the key to the ancient mystery of muscular contraction.

Living organisms resist degeneration and destruction with the help of muscles, and biochemists had long believed that a hypothetical *inogen* provided the energy required for the flexing of muscles at work.

Two researchers at Cambridge University in United Kingdom confirmed that lactic acid is formed when muscles contract and Otto Meyerhof of Germany showed that this lactic acid is a breakdown product of glycogen, the animal starch stored all over the body, particularly in liver, kidneys and muscles. When Professor Archibald Hill of the University College of London demonstrated that conversion of glycogen to lactic acid partly accounts for heat produced during muscle contraction everybody assumed that glycogen was the *inogen*. And, the 1922 Nobel Prize for medicine and physiology was divided between Hill and

Meyerhof.

But how is glycogen converted to lactic acid? Embden, another German biochemist, advanced the hypothesis that blood sugar and phosphorus combine to form a hexose phosphoric ester which breaks down glycogen in the muscle to lactic acid.

In the midst of the insulin experiments, it occurred to Fiske and SubbaRow that Embden's hypothesis would be supported if normal persons were found to have more hexose phosphate in their muscle and liver than diabetics. For diabetes is the failure of the body to use sugar. There would be little reaction between sugar and phosphorus in a diabetic body. If Embden was right, hexose (sugar) phosphate level in the muscle and liver of diabetic animals should rise when insulin is injected. Fiske and SubbaRow rendered some animals diabetic by removing their pancreas in the spring of 1926, but they could not record any rise in the organic phosphorus content of muscles or livers after insulin was administered to the animals. Sugar phosphates were indeed produced in their animals but they were converted so quickly by enzymes to lactic acid that Fiske and SubbaRow could not detect them with methods

then available. This was fortunate for science because, in their mistaken belief that Embden was wrong, they began that summer an extensive study of organic phosphorus compounds in the muscle “to repudiate Meyerhof completely”.

The departmental budget was so poor that SubbaRow often waited on the back streets of Harvard Medical School at night to capture cats he needed for the experiments.

When he prepared the cat muscles for estimating their phosphorus content, SubbaRow found he could not get a constant reading in the colorimeter. The intensity of the blue colour went on rising for thirty minutes. Was there something in muscle which delayed the colour reaction? If yes, the time for full colour development should increase with the increase in the quantity of the sample. But the delay was not greater when the sample was 10 c.c. instead of 5 c.c. The only other possibility was that muscle had an organic compound which liberated phosphorus as the reaction in the colorimeter proceeded. This indeed was the case, it turned out. It took a whole year to isolate and identify this compound.

The mysterious colour delaying substance was a compound of phosphoric acid and creatine and was named phosphocreatine. It accounted for two-thirds of the phosphorus in the resting muscle. When they put muscle to work by electric stimulation, the phosphocreatine level fell and the inorganic phosphorus level rose correspondingly. It completely disappeared when they cut off the blood supply and drove the muscle to the point of "fatigue" by continued electric stimulation. And, presto! It reappeared when the fatigued muscle was allowed a period of rest.

Phosphocreatine created a stir among the scientists present when Fiske unveiled it before the American Society of Biological Chemists at Rochester in April 1927. Phosphocreatine created a stir among the scientists present when Fiske unveiled it before the American Society of Biological Chemists at Rochester in April 1927. The *Journal of American Medical Association* hailed the discovery in an editorial. The Rockefeller Foundation awarded a fellowship that helped SubbaRow to live comfortably for the first time since his arrival in the United States. All of Harvard Medical School was caught up with an enthusiasm that would

be a life time memory for con-temporary students. The students were in awe of the medium-sized, slightly stoop shouldered, “coloured” man regarded as one of the School’s top research workers.

SubbaRow’s carefully conducted series of experiments disproved Meyerhof’s assumptions about the glycogen lactic acid cycle. His calculations fully accounted for the heat output during muscle contraction. Hill had not been able to fully account for this in terms of Meyerhof’s theory. Clearly the Nobel Committee was in haste in awarding the 1922 physiology prize, but the biochemistry orthodoxy led by Meyerhof and Hill themselves was not too eager to give up their belief in glycogen as the prime source of muscular energy.

Fiske and SubbaRow were fully upheld and the Meyerhof-Hill- theory finally rejected in 1930 when a Danish physiologist showed that muscles can work to exhaustion without the aid of glycogen or the stimulation of lactic acid.

Fiske and SubbaRow had meanwhile followed a substance that was formed by the combination of phosphorus, liberated from phosphocreatine, with an unidentified compound in muscle. SubbaRow isolated it and identified it as a chemical in which adenylic acid

was linked to two extra molecules of phosphoric acid. By the time he completed the work to the satisfaction of Fiske, it was August 1929 when Harvard Medical School played host to the 13th International Physiological Congress. ATP was presented to the gathered scientists before the Congress ended. To the dismay of Fiske and SubbaRow, a few days later arrived in Boston a German science journal, published 16 days before the Congress opened. It carried a letter from Karl Lohmann of Meyerhof's laboratory, saying he had isolated from muscle a compound of adenylic acid linked to two molecules of phosphoric acid!

While Archibald Hill never adjusted himself to the idea that the basis of his Nobel Prize work had been demolished, Otto Meyerhof and his associates had seen the importance of phosphocreatine discovery and plunged themselves into follow-up studies in competition with Fiske and SubbaRow. Two associates of Hill had in fact stumbled upon phosphocreatine about the same time as Fiske and SubbaRow but their loyalty to Meyerhof-Hill theory acted as blinkers and their hasty and premature publications reveal their confusion about both the nature and significance of

phosphocreatine.

The discovery of ATP and its significance helped reveal the full story of muscular contraction: Glycogen arriving in muscle gets converted into lactic acid which is siphoned off to liver for re-synthesis of glycogen. This cycle yields three molecules of ATP and is important in delivering usable food energy to the muscle. Glycolysis or break up of glycogen is relatively slow in getting started and in any case muscle can retain ATP only in small quantities. In the interval between the beginning of muscle activity and the arrival of fresh ATP from glycolysis, phosphocreatine maintains ATP supply by re-synthesizing it as fast as its energy terminals are used up by muscle for its activity.

Muscular contraction made possible by ATP helps us not only to move our limbs and lift weights but keeps us alive. The heart is after all a muscle pouch and millions of muscle cells embedded in the walls of arteries keep the life sustaining blood pumped by the heart coursing through body organs. ATP even helps get new life started by powering the sperm's motion toward the egg as well as the spectacular transformation of the fertilized egg in the womb.

Archibald Hill for long denied any role for ATP in muscle contraction, saying ATP has not been shown to break down in the intact muscle. This objection was also met in 1962 when University of Pennsylvania scientists showed that muscles can contract and relax normally even when glycogen and phosphocreatine are kept under check with an inhibitor.

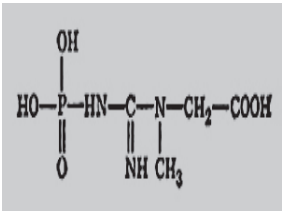
* * *

SubbaRow now busied himself completing his thesis and course credits for the Harvard PhD. It was over six years since he had left home promising his wife he would be back in three years. But he gave no thought to return to his homeland and waiting wife.

Seshagiri had been upset at the parting by SubbaRow's failure to say tile customary words, "I will come back". And she had written soon after SubbaRow arrived in Boston impatient letters asking him to return at the end of the first year. A woman in her time and situation could alone appreciate Seshagiri's mental agony. And she for her part could not understand SubbaRow's zeal for science and research, suffering all the tensions of a

life with a menial hospital job that provided hardly enough to eat and left little energy and time for studies. No wonder they exchanged letters that only added to their suffering.

When they parted, Seshagiri was expecting their child in six months' time. The child, a son, was born prematurely and the concern SubbaRow expressed for Seshagiri's health helped bring about a temporary reconciliation. But his indifference to the birth and the death within a year of the boy naturally annoyed Seshagiri somewhat. But the real trouble began toward the end of 1925 when a Rockefeller fellowship was in sight. SubbaRow wrote home that he wanted to get his wife over and stay five or six years more in USA to complete research on hand and take up new challenges in research. Her father did not know how he could send Seshagiri to Boston. His fear that SubbaRow would forsake his wife increased. He wrote a letter in which the word "cheating" slipped in. SubbaRow could not agree that extension of his stay to complete education



amounted to cheating, and replied, “Let me choose my career without interference.”

SubbaRow wrote home less and less as his research work proceeded from insulin to phosphocreatine to ATP, and all his spare time was used to complete courses on which Harvard insisted for awarding the PhD. Seshagiri’s distress voiced in her letters disturbed SubbaRow but he felt she was quite unreasonable to break his concentration of mind on research problems. Although the phosphocreatine discovery was a major factor in his favour, SubbaRow got the Rockefeller fellowship only after the Rockefeller Foundation decided in 1927 to help Government of India set up the All India Institute of Hygiene and Public Health in Calcutta. For, it was the Foundation’s policy to award fellowships to non-Americans only if they had assurance of a position in their home country. At the suggestion of the Foundation, SubbaRow applied for the biochemistry professorship at Calcutta and wrote home he will return if he got the job. SubbaRow was interviewed in Boston by officials of the Indian Medical Services visiting USA for negotiations with the Rockefeller Foundation. He was told by them that the

biochemistry chair was reserved for an Englishman, and he rejected the alternative jobs they offered him.

SubbaRow passed one by one the chemistry and language courses no way related to his biochemical research but considered by Harvard to be necessary for the academic training of its "Doctors of Philosophy". He was allowed to take the final examination in February 1930. He passed it with "honours" and got his scroll at the Harvard convocation on June 19.

The British medical authorities were even then reluctant to make him the professor of biochemistry at the Calcutta institute. They were jealous of their right to make appointments and guarded it against encroachment by the Rockefeller Foundation. The dispute between those who financed and those who administered the institution was later settled and SubbaRow was offered the professorship.

A cautious SubbaRow asked for freedom to pursue research without interference even by the Director of the Institute. As no such guarantee came forth, he did not make the formal application when the professorship was finally advertised in March 1935. He was by then very much involved in the job of isolating from liver

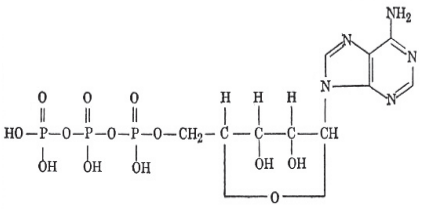
the vitamin that would, it was then believed, cure not only pernicious anaemia that afflicted many Americans but tropical sprue which had afflicted all the Yellapragada brothers and carried away Purushottam, the eldest of them.

Long before this, SubbaRow had virtually broken his ties to Seshagiri with a letter to her father saying, "I love Seshagiri but I cannot sacrifice everything I am doing here now and rush home . . . I love my science more than any other thing in the world. When you think of me, remember that education and research are my highest ambitions in life. Then come my family, my mother and my brother. Anything which comes in the way . . . I have to push aside."

When he later landed a well paying research job, SubbaRow paid back his father-in law with interest all the money he had received for his education and sent also a big remittance to Seshagiri informing her he had annulled their marriage and remarried. He also sent her quarterly remittances presumably in payment of alimony. It was only when he died and what he left behind was divided between Seshagiri and Venkamma that the family learnt SubbaRow had neither annulled his marriage nor remarried.

SubbaRow had by turning back on family life sought

to make the whole world his family. Seshagiri made her immediate family — parents, brothers, sisters, nephews and nieces — her whole world. A generous hearted aunty can indeed be helpful in several ways. She spoke once philosophically: “I always hoped that he would come back, that God will reunite us one day . . . I suffered from the pain both of separation and of yearning for reunion. It is my misfortune that he never came back. But our marriage served to fulfil the mission of his life.”



# On the Track of Brother's Assassin

Persons suffering from anaemia are pale because their blood is short of red cells and haemoglobin, get easily tired, and are breathless when tired. They are found among both the well-fed and the under fed. For it is not enough to eat right. What is eaten should be digested for the body to get what is needed to manufacture healthy blood. There are many kinds of anaemia and two of them, pernicious anaemia and tropical sprue, are so alike in symptoms and signs that medical men then believed they had a common cure. Yet pernicious anaemia affects the well fed when their stomach wall degenerates and is unable to absorb from their food a vitamin needed for the building of healthy red blood cells and haemoglobin whereas tropical sprue affects the poor whose food lacks two essential vitamins.

Two Boston physicians, George H Minot and William P. Murphy, in 1926 found that a daily meal of broiled liver brings about miraculous cures in pernicious anaemia patients. But the patients lack appetite and the doctors had difficulty force feeding them. Drs. Minot

and Murphy therefore went to Dr. Edwin J. Cohn, authority on protein chemistry at Harvard Medical School, for help to extract from liver the substance that cured pernicious anaemia.

SubbaRow was introduced to Gordon A. Alles, an assistant of Cohn, one evening in September 1927 in the dining room of his hostel. Over the meal, they discussed their methods for removing protein from liver: SubbaRow before extracting phosphorus compounds and Alles before extracting the anaemia-curing substance. The two met regularly thereafter. By and by their interest shifted from techniques to objectives. Alles got interested in insulin research on which SubbaRow had previously worked. SubbaRow was moved by a desire to isolate the cure for pernicious anaemia and tropical sprue. But SubbaRow realised it would not be morally right for him to work in competition with a fellow research group in the Harvard Medical School.

When SubbaRow and Alles discussed this moral issue, Bernard Jacobson, a medical student helping SubbaRow with phosphocreatine work, suggested a solution. Cohn had by then removed a large part of the

material in liver that was useless against pernicious anaemia and had each new extract from liver tested among the patients of Minot and Murphy. The daily liver dose for patients had got considerably reduced but the isolation of the cure in its pure form was still far away. Suppose SubbaRow used animals to test liver extracts instead of human patients, Jacobson asked. He would not be competing then with Cohn. He might on the other hand speed up the search for APAF, the anti pernicious anaemia factor. Fiske said he would have no objection if SubbaRow pursued APAF on his own with such time, funds and facilities as could be spared from the official research project on phosphorus compounds.

SubbaRow jumped into Jacobson's car and they returned from the slaughterhouses with a supply of liver that the butchers were glad to get rid of at a special price. SubbaRow heated and boiled liver with chemicals and came up with solutions of different colours and smells. Jacobson fed them to guinea pigs, drew blood, smeared glass slides and counted red blood corpuscles under a microscope.

Alles soon went to California for insulin research that

has made daily injections safer for diabetics, and Cohn himself left liver research in 1930 after producing a liver extract that could be given to patients as an injection.

SubbaRow's own liver extraction work had progressed slowly in the first few years because of his and Jacobson's preoccupations with their regular academic duties. By the time Cohn retired from the race for APAF, SubbaRow got his PhD and Jacobson was settled in Massachusetts General Hospital with a research fellowship.

Jacobson could now test in pernicious anaemia patients admitted to his hospital the liver extracts that were found to boost red blood corpuscles in guinea pigs. When a 3 mg fraction brewed by SubbaRow from a hundred grams of fresh liver radically improved the blood picture of the animals, they were excited thinking they had reached their goal.

But the liver concentrate so potent in guinea pigs was worthless in patients. The animal test as a guide to the isolation of APAF had to be abandoned. Not discouraged, SubbaRow turned to the solution from which he had precipitated the concentrate. It was active in patients. SubbaRow added a small amount of

charcoal to decolourise this solution before harvesting a crystalline material from it. The crystals were only a third as active as the solution before it was decolourised. Instead of blaming charcoal for the big loss of activity, SubbaRow reasoned that charcoal had perhaps soaked up all that was good in liver for Jacobson's patients. If his guess was right, he had indeed made a breakthrough in the search for APAF. In order to test this, he had to extract what had got bound (adsorbed) on to the charcoal surface. It took weeks to test each one of the possible extractors with the equipment SubbaRow fabricated himself.

SubbaRow was engrossed in this work one sunny morning in April 1934 when a young German girl walked into his life like "a breath of fresh air" and literally shook him out of his leisurely pace of research. Fiske brought her into the laboratory, said she was Dr. Vilma Prochownick who would be his new assistant and was gone after a few more words of introduction. SubbaRow had greeted her with a warm smile but said nothing after they were left alone. "I need a lot of your

help and patience," Miss Prochownick said breaking the silence. "I have never worked in this field and I am a stranger in this country." "Oh," he said with the friendly smile reappearing on his face, "I know how you must feel. When I came to this country several years ago, I felt the same way."

He got up and took her around the Harvard Medical School buildings. They talked of her background and the problems of her work with him.

Vilma's father was a judge pensioned off in Hamburg when Hitler came to power the year before. She had got her PhD in organic chemistry only a few weeks earlier after doing work on a wood-cracking process which could be used for making animal feed in times of war. Afraid her work would be seized by the Nazis and she herself made a virtual prisoner, she had obtained a visitor's visa with the help of a friend at the American Consulate in Hamburg and left suddenly for New York. She carried a letter from a former professor to James Conant, President of Harvard University, who as a student in Germany had often been a weekend guest at the professor's family estate. Mr. Conant received her cordially, approved her desire to use her

chemistry background in the service of medicine and sent her with a note to Fiske who was then acting as head of biochemistry department. She had been brought immediately over to SubbaRow.

Vilma was soon working as SubbaRow's laboratory assistant and the laboratory's housekeeper. SubbaRow kept dogs in the laboratory to test liver extracts against black tongue disease in dogs, and the dogs kept the laboratory floor always dirty. An Irish woman came once a week to clean the floor but the walls and ceiling of the laboratory remained full of cobwebs. The German dislike of disorder made Vilma rebel against this, and she took up the chore of keeping the laboratory clean when the Irish woman suddenly died a few months later.

Vilma was also used to well equipped German laboratories and was exasperated SubbaRow was not bothered about the equipment which contributed so much to his slow progress with charcoal extraction. She suggested vacuum pumps for his distillation equipment. "What is the hurry with the distillation," he asked. "It gives me time to think and read." She discussed it with Fiske and was told Harvard was hit

by the depression in the American economy and could not increase the budget of the department. Her enthusiasm toned up SubbaRow and the work was speeded up. SubbaRow found in September that the common ethyl alcohol was best for extracting the stolen liver fraction from charcoal.

The recovered liver fraction was consistently beneficial to Jacobson's patients; and another liver concentrate cured the dogs of G B Schnelle, a Boston veterinarian, of black-tongue.

Vilma began the chemical analysis of both the potions. In the winter of 1934, amidst all the excitement in the laboratory of SubbaRow, there came a visitor to Fiske. This was Dr. Guy W. Clark of Lederle Laboratories, a pharmaceutical company of Pearl River in New York State. He had been helped by Dr. Murphy of Peter Bent Brigham Hospital in 1933 to market a liver injection for pernicious anaemia patients. The "Lederle 3 C.C. Parenteral" had been approved by the American Medical Association's Council on Pharmacy and Chemistry but was found, amidst much professional enthusiasm, to develop sediment. Clark rushed to Murphy and was referred to Fiske. He cautiously asked

Fiske if he could be of any help to SubbaRow in his efforts to “unravel liver”.

Fiske remembered Vilma’s demand for vacuum pumps and said, “Why don’t you? Here he is cooking up to 30 to 40 pound of liver under great difficulty while you have all sorts of equipment at Lederle.”

Under an informal arrangement they worked out, Clark secured technical advice from SubbaRow in return for a steady supply of crude liver extracts and vacuum pumps Vilma desired for the distillation equipment.

SubbaRow’s work had so remarkably reduced liver extract doses for Jacobson’s patients that they felt justified publishing what they had accomplished. Jacobson first reported his clinical results in a series of papers to the American Society for Clinical Investigation. Then they had a comprehensive paper published in the April 11, 1935 issue of the ***New England Journal of Medicine***. The paper was signed by SubbaRow and Jacobson as well as Fiske in whose department the liver fractionation work had been done. Schnelle was cited as collaborator in the section of the paper dealing with animal experiments and V. Prochownick PhD in sections discussing the clinical

nature of the liver extracts.

Black tongue in dogs and pellagra in humans are caused by the same food deficiency, and SubbaRow decided to take the liver extracts that had cured Schnelle's dogs to Birmingham, Alabama, to be tested by Dr. Tom Spies who had a special clinic there for the care and treatment of pellagrins. Birmingham was a strictly segregated city in the deep south of USA. Knowing SubbaRow would be hurt at being mistaken for a Negro, Vilma suggested his wearing a turban. But SubbaRow went off saying, "Spies has made reservations for me in one of the leading hotels, telling them that a distinguished East Indian scientist from Harvard is visiting Hillman Hospital."

It was next the turn of SubbaRow to worry about Vilma. Her visitor visa was expiring. To stay on, she had to re enter the United States as a legal immigrant from another country. They secured her an invitation to give a lecture on her wood cracking process at the University of Montreal. This gave her the official stamp for a visit to Canada. To make her return possible, Harvard Medical School gave her a letter saying her fellowship would be renewed for another year. And yet when she left for

Montreal, SubbaRow worried if the American Consulate would demand additional documents, leaving Vilma no alternative but to return to Germany. They had been drawn close during the twelve months of hard work on black tongue fractions of liver and feared the possibility of abrupt separation. Their fear revealed the mutual concern of two souls who by their very differences in temperament so complemented each other. They had a certain similarity in outlook and the bond of common scientific interests. Above all they had a feeling -each was needed by the other. Vilma felt he needed an intimate friend on whose devotion he could always rely and thought she could be that friend. SubbaRow thought she as a refugee needed all the protection he could give her. After two tense days, Vilma phoned from Montreal that the Consulate had issued her the immigrant visa. SubbaRow was overjoyed. Not long after Vilma's return, Jacobson presented to the Society for Clinical Investigation data on a little brown 1 c.c. water solution of three crystalline liver fractions derived from, and as effective as, 100 gm's of the original Minot and Murphy prescription of raw liver. It had only 12 to 15 mg of solids compared to 180 m.gs in previous

preparations and could be administered as an injection with considerably reduced risk of adverse reaction.

A month later, in June 1935, Clark brought on market the 'Lederle 1 C.C. Liver Extract' for treating pernicious anaemia patients and a 'Lederle Hepatic Extract' for treating dogs suffering from black-tongue. Vilma was delighted that SubbaRow's work, which she had assisted and helped speed up, had yielded preparations that were getting into general medical practice. Their joint work on the anti pellagra vitamin was about to reach a critical stage. SubbaRow came to be convinced at this time that he had no future at Harvard and planned to leave. He promised to take Vilma along as an assistant and she decided to take additional summer courses to be more useful to him. Before she could enrol herself in the courses, Vilma was stricken with a pulmonary infection. SubbaRow put her in a sanatorium at Sharon near Boston and visited her every Saturday. His dedication to her touched their many colleagues. But Vilma, touched as she was by his caring so much for her happiness and well being, felt uncomfortable about having become a burden on him. Somehow the sense of fun they had while working

together in the laboratory evaporated during her long illness.

She was still in the sanatorium in August 1936 when SubbaRow sent out for publication a report on Fraction I, which she had helped partly identify and which brought about blood regeneration In Jacobson's patients in 0.7 mg daily doses.

She returned to work after a few months but late in 1937 she suffered a relapse and was advised to take a year's change of climate. SubbaRow suggested a sanatorium in the Adirondacks Mountains where SubbaRow could plan his summer vacations. She opted, against his opposition, for the National Jewish Hospital in distant Denver suggested by a physician uncle come over from Germany and settled in New York City.

Life for SubbaRow centred again on the laboratory and their correspondence suffered. He did write to her to work part time in the sanatorium laboratory but there was no position there for her. He subscribed to the

***Annual Review of Biochemistry*** for her. She memorized the first few volumes but her heart was no longer in biochemistry. She lacked the daily stimulation of laboratory work and personal conversations. The tempo changed in the timeless world of patients living isolated from the outside world and she began to develop a totally different set of values. She read English literature voraciously and jumped at the chance when the sanatorium director asked her to organise the medical library.

SubbaRow was shocked when Vilma wrote she felt she should acquire a degree in library science. He wrote back angrily she would be wasting a long education in chemistry. She agreed but felt she had no choice. Once she made the decision, he never wrote her again.

SubbaRow went to Pearl River each Friday evening to use the huge Lederle liver plant normally idle over the weekend. For two days Guy Clark's men processed half a ton of liver as directed by SubbaRow. Back in Boston on Monday morning, SubbaRow worked hard till Friday evening on fractionating the liver concentrates brought from Pearl River in a couple of gallon jugs. But nothing more than a refinement here and there in technique and a little jump now and then in the liver

extract potency was achieved in spite of all the energy and time he expended, in spite of all the devotion of men at Pearl River who sacrificed their weekends along with him, in spite of all the facilities and the funds the big corporation provided. Fraction I represented the ultimate in the concentration of APAF with the analytical techniques then available.

SubbaRow in the mean time applied his analytical mind to the problem of isolating APAF. Jacobson's clinical trials had been showing that certain liver fractions inactive by themselves brought about in patients a response approximating that of crude liver if administered along with the main active liver fraction. Five of the chemically distinct compounds isolated by SubbaRow from liver were found by Jacobson to have this power to augment the activity of Fraction I.

SubbaRow and Jacobson in a 1937 paper designated Fraction I the primary factor and the chemicals which augmented its action the accessory factors. A year later in a paper prepared for a German journal SubbaRow advanced his "multiple factor hypothesis": The active liver preparations reported by him and his rivals in the race for APAF had differing chemical properties. This

had cast a doubt whether pernicious anaemia was caused by the lack, and hence would be cured by the administration, of a single substance. There was a possibility that the effective cure of pernicious anaemia rested on the interaction of several factors as was demonstrated by the augmentative action of their accessory factors on the primary factor. Jacobson presented their "multiple factor therapy" to the American Medical Association at its 1940 session in New York. The rival liver groups could only agree that the isolation of APAF in its pure crystalline form alone would prove or disprove the hypothesis. None of the participants had any idea that APAF was present in liver not in milligrams but in micrograms. Fraction I had reduced liver doses by 100,000 times. Less than a milligram of it was as effective as the original daily dose of l00 grams of raw liver. But there are a thousand micrograms to a milligram! It would be another eight years before new micro techniques would finally zero in on the elusive APAF.

SUBBAROW had over the years become something of an institution within the Harvard Medical complex. Because of his contributions to the unravelling of the

mysteries of muscular contraction and toward the isolation of APAF, he was highly esteemed and treated with friendly respect by the Faculty. His dedication to work, his broad knowledge and his willingness to talk inspired students and many of them came to him to discuss and plan their work. Many of them worked for him, doing a piece of research while they were in medical school. A lot of them felt their life was touched — enriched - because of their contacts with him.

But the best position that Harvard could offer SubbaRow for almost a decade was that of a Teaching Fellow, the lowest staff position usually reserved for outstanding post graduate students needing financial support.

SubbaRow had got it while he was himself a postgraduate student. But Folin could not promote him even after the phosphocreatine and ATP work was well behind and he had secured the PhD. By allowing him to remain at the biochemical laboratory, Harvard did help him “to advance knowledge”. Any attempt by Folin to entrust student instruction to SubbaRow would however have shocked the Faculty of that time. So rather than attempt to promote him to Instructor, Folin

excused him from the duties of a Teaching Fellow to teach, "permitted" him to work full time in the laboratory, and saw to it that his salary was raised. All this appeared merciful to SubbaRow. The alternative was to return to India where he might get a better academic position but not an opportunity for the kind of research he had set his heart on.

When Folin died suddenly in October 1934, Fiske was made the acting head of the department. A proposal that he be made the joint head along with Edwin Cohn was however not acceptable to the Faculty. Fiske was known to have a heart condition and to suffer from depression because he felt he was cheated by the Europeans of the credit for phosphocreatine and ATP discoveries. In this condition, he had not allowed SubbaRow for years to publish the work he did in his laboratory on the phosphorus compounds in liver and other organs. He said the work should be brought together in a book provisionally titled "Phosphorus Compounds" instead of being published piecemeal but months passed without his starting on the proposed book. It was then that SubbaRow had devoted himself first increasingly, and then entirely, on the isolation of

APAF from liver.

Now acting head, Fiske did not show up at the Department for long periods of time and when he came he sat in his room without- working. Worried because her husband's promotion was at stake, Mrs. Fiske discussed the situation with SubbaRow. SubbaRow began attending to Fiske's administrative and other work. Despite his best efforts to cover up, Fiske's condition could not be kept hidden completely. Some in the Faculty talked about Fiske being unapproachable, how nobody could work with him and how his contribution to research was minimal.

When he heard of this last, SubbaRow wrote immediately to President Conant of Harvard saying there was no truth in the "rumour" that the phosphorus method, phosphocreatine and ATP were mostly his work. He had merely been an "extra pair of hands" for Fiske, and his contribution was mostly technical work. "The brains behind the work as well as the finer side of the technique are entirely Professor Fiske's," he wrote. SubbaRow was being loyal to one under whom he had trained and done such fruitful research. He was being generous as well to Fiske whose years of scientific

research were now behind.

SubbaRow's sacrifice was all in vain. Conant brought in his old friend, Professor A. Baird Hastings, from the University of Chicago as head of the HMS Department of Biochemistry. He however made Fiske a full professor but saw no reason to include the self confessed technical hand of Fiske in the list of departmental promotions.

If SubbaRow had considered he could afford to sacrifice credit for past research in view of the breakthrough he had at this time achieved in the search for APAF in liver, he could not have been prepared for this consequence. In his lowly staff position, he could never hope to get funds and facilities for success in research. It was in these circumstances that he had discussed with Vilma about taking a position outside Harvard. Vilma's illness and departure from Boston upset these plans. Moreover, learning of SubbaRow's intentions, Conant promoted him to Instructor in September 1936 and more than doubled his salary. Hastings, the new departmental chief, recognised in SubbaRow "a most brilliant and dedicated biochemist", asked him to take classes for medical students but was handicapped in providing

the facilities for the success of his research since he was, even as Instructor, not a member of the Faculty.

SubbaRow did not have working with him even one post graduate student let alone a group so essential for cross-fertilisation of ideas in research. His assistants were students with medical careers ahead but glad to work part time in his laboratory for the fellowships that helped to support them through the medical school. His liver supplies were dependent on an outside corporation, and his collaborators were outsiders on whose methods and procedures -he had no control. And, after Vilma left, he depended on a commercial laboratory in a far-off town for the analysis of new liver fractions.

The limitations of such an arrangement became glaring when SubbaRow took up the search for other vitamins, besides APAF, in liver.

He lost the race for pantothenic acid, the vitamin of 'eternal youth', to Dr. Roger J. Williams of the University of Texas. Even more tragic were the circumstances under which Conrad A. Elvehjem of the University of Wisconsin beat SubbaRow in the discovery of nicotinic acid as the vitamin that cured pellagra. A group at Duke

University in Durham, North Carolina, just neglected to test in black tongued dogs the sample of nicotinic acid that SubbaRow had isolated from liver and sent them. One of his Durham collaborators could not substantiate his report that another chemical isolated by SubbaRow from liver also cured black tongue in dogs and he and SubbaRow were forced to publish a retraction of the claim.

Tom Spies, the renowned vitamin hunter who had off and on collaborated with SubbaRow, attributed the trouble to Harvard Medical School's denial of the "cooperation, facilities and personnel" SubbaRow needed. He invited SubbaRow to join his medical group at the University of Cincinnati. When SubbaRow declined, he wrote to Hastings demanding that Harvard should either release him or give him the required facilities.

Hastings stirred himself to the extent of opening the Faculty doors and making SubbaRow an Associate in September 1938. He also proposed to the Dean of Harvard Medical School a "Nutrition Project" that would ensure a proper budget and collaborators for SubbaRow. This would help improve teaching of

nutrition to medical students and make the Medical School a rallying point for nutrition research then being carried out in different parts of the University.

Nothing came of the Nutrition Project. SubbaRow was now receptive to the urging of Clark that he leave Harvard to organise research at Lederle Laboratories. William Bell, president of American Cyanamid, was surprised the man responsible for the profitable liver extracts business of his Lederle Laboratories division was not on the "company payroll". He felt the division's future was threatened by synthetic vitamins and sulphonamides, the new drugs for fighting infections diseases. The patents were controlled by drug company giants. He told SubbaRow he would give him without question whatever money, men and building space he asked for creating at Pearl River a research organisation that would keep his pharmaceutical division alive and prosperous.

Bell's original offer included an annual salary of $14,000 compared to the $2700 he was getting at Harvard. SubbaRow said he would take only half of the offered salary if a new research building was constructed for him. Bell readily agreed. SubbaRow said he would

move out of Harvard when the building was ready in May 1940.

Hastings and others at the Medical School assumed SubbaRow was leaving because of the money the pill rollers could afford to pay him. William Berenberg, who had previously helped in the laboratory, teased him: "Finally, you have seen the light. You are willing to take a job that will pay you well. Maybe you have your own catalogue now and will be able to get some of those things that you have missed in life."

"I am going," SubbaRow replied, "because I have a feeling that this is an opportunity to be creative in a laboratory. It is not so much finances for personal benefit as it is a chance to work without having to be concerned about budgets."

Seventeen years of ascetic life at Harvard had served the purpose of rigorous self education. The time had come for him to "return" to the workaday world and to put his knowledge to work for the welfare of humanity.

# The Battle Royal

**When SubbaRow** called on James Conant before leaving for Lederle, the Harvard president said, "You know if you ever wish to return to Harvard, you certainly will be able to do so."

SubbaRow, because of his association of five years as a consultant to Lederle was fully aware of the hazards involved in the step he was taking. He had taken it because his employers' desire to maintain their place in the drug industry rocked by a scientific revolution coincided with his ambition to conquer diseases. He did not worry how he was going to get a new job if he failed. He was confident he was going to be indispensable to the man who had hired him, and had faith in the man's assurance of support to the kind of research he planned.

His faith in William Brown Bell, a soft-spoken puny little lawyer who built a small fertilizer company called American Cyanamid into a great chemical combine, was not misplaced. This shrewd business manager dared to dream in terms of chemistry and believed, like the

one satirised in ***Punch***, that research "does no harm. It reduces unemployment. Visitors and shareholders are impressed by the sight of so much science and the smell of so much sulphurated hydrogen. Someone may find that something which will make all the difference in your business. Scientists are nice, quiet lads with no vice."

After expanding American Cyanamid activities from fertilizers into industrial and organic chemicals, colours and plastics, William Bell set his sight on drugs. After buying a surgical suture firm, he negotiated the acquisition of Lederle Antitoxin Laboratories which was under the charge of his elder brother, Frederic.

Frederic Bell was an auditor who in 1904 left the New York Health Department along with Dr. Ernst Joseph Lederle, the Health Commissioner, to organise a laboratory for "chemical, bacteriological and sanitary investigations and analysis". Two years later, they induced Dr. William H. Park, who had developed an improved method for making diphtheria antitoxin, to

leave the Health Department to set up a new venture, Lederle Antitoxin Laboratory. As they took up the manufacture also of the tetanus anti toxin and small pox vaccine and orders increased, production was shifted to pretty Pearl River village in the rolling hills of fruit and vegetable growing Rockland County.

Frederic Bell succeeded as president of the Company three years later when Dr. Lederle was reappointed Commissioner of Health of New York City and had to give up his share holdings in the company. A pharmaceutical section was added in the early twenties and Guy Clark, brought in from University of California in 1927, launched the company into the liver extracts business using waste liver from the hog cholera serum plant.

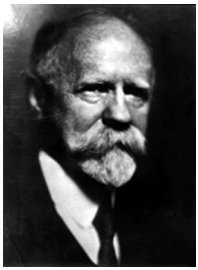
When Frederic agreed to William's proposal for an exchange of stock and the company became a subsidiary of American Cyanamid in February 1930, the word "Antitoxin" was dropped from its name since the company now had a wide range of products.

William Bell became president in July 1931 when Frederic died in an automobile accident. American Cyanamid's financial backing helped Lederle Laboratories to survive the Great Depression when

thousands of American businesses collapsed.

Bell wished in 1934 that Lederle should resume production of scarlet fever antitoxin and hired Dr. Wilbur G. Malcolm who was making one with high potency for a government laboratory in Massachusetts. The scarlet fever business turned out to be unprofitable but Malcolm was retained because he came up with the idea that rabbits could replace horses for producing pneumonia antisera.

Bell built the largest rabbit warren in the world only to write off the big investment on research facilities and rabbits because of the introduction of sulpha drugs which cured pneumonia and replaced sera. What now saved Malcolm was the foresight in keeping himself posted on sulpha research at Stamford and Calco divisions of American Cyanamid and arranging Lederle to be ready for the evaluation job when research yielded some nine sulpha drugs.



Malcolm knew that his own background in antitoxins and vaccines was not going to be of much value in the new pharmaceutical world of vitamins and antibiotics.

He knew that his own genius lay not so much in directing research as administering research people. He was therefore as enthusiastic as Bell about getting SubbaRow to direct research. The arrival of SubbaRow in May 1940 completed the triumvirate that transformed Lederle into a leader in the drug industry in less than ten “golden” years. Bell was the provider, counsellor and appraiser, Malcolm was the custodian of the physical facilities, and SubbaRow was the genius on whose counsel the two depended on programming research and staffing the research laboratories.

Bell did not however give SubbaRow the overall charge of Lederle research straightaway. He only made him one of the three Associate Directors of Research. He anticipated a great demand for biologicals (anti toxins and vaccines) in view of war in Europe and considered it wise to leave the biological department in charge of Dr. Austin Joyner who had been with the Rockefeller Institute and an assistant professor at the University of Alabama. And it would not have done to put the famed Dr. Ralph Wyckoff, in charge of virus research, under

anyone. SubbaRow was given charge of chemical and pharmaceutical research which was the department with a future and the one on which depended the fortunes of Lederle.

Malcolm as Director of Laboratories was in charge of the entire operation at Pearl River. He and SubbaRow quickly established a relationship that was marked by deep friendship and mutual respect. Malcolm would fight the money battles for research with the Cyanamid executives at New York, but SubbaRow could go to Bell himself if that became necessary.

It was a fortunate circumstance for SubbaRow that Bell was very enthusiastic about modern research, which he considered more or less a gamble but a risk that a modern company should take. He once said the formula for success in this gamble was to select a top chemist and "lock him up in a room after carefully removing everything from the room except a desk, a chair and an idea". SubbaRow must have often wished Bell would just do this and let him alone with his research. But Bell kept up a steady stream of new ideas he wanted Lederle to take up. He picked up his ideas from a variety of sources: physicians attending on sick

relatives, members of the staff who combed newspapers and journals, and all kinds of persons, not all well intentioned, trying to take advantage of his enthusiasm. SubbaRow did not allow the stream of notes from Bell, mostly routed through Malcolm, to sweep him off his feet. His reaction would be something along the lines of a "No reply necessary" that he once scribbled across a memo suggesting a programme to isolate a "rice factor" that may be beneficial to those with high blood pressure. Bell knew this and took it in good humour. "If I occasionally threaten the freedom of scientific thought by suggesting a bright idea for a research project," he once told a group of industrial chemists, "it is promptly but tactfully treated with the contempt it deserves. However I refuse to believe that these suggestions do much harm."

On balance it was an asset to have such an enthusiastic research promoter as Bell to back him. But SubbaRow was in no mood to suffer imposition by other Cyanamid executives who tried to imitate Bell. He sharply reacted to one of them with a note saying, "The philosophy of all work for the other fellow and all suggestions for oneself is a favourite pastime of many."

SubbaRow could get away with this and other angry notes because Lederle could ill afford to lose him at a time the industry was being rocked by an unending stream of vitamin and antibiotic discoveries. Neither Bell nor even Malcolm could quite comprehend the developing situation. Bell wrote on a report from SubbaRow: "Unfortunately I am out of my depth in discussing details but I can in a general way appreciate the importance of what Dr. SubbaRow says." That was sufficient for SubbaRow to get all the financial and moral backing he needed to carry forward his research programme. Bell would often draw more optimistic conclusions from SubbaRow's progress reports than the latter felt called for. SubbaRow once warned him that he had "no promising lead" as Bell thought on a particular research problem but only wanted "to try a few crazy ideas that I have". Bell returned the note to SubbaRow with the pencilled observation: "The old complaint! Palissy, Goodyear, Morse, Ehrlich, and Frasch to name a few of the craziest had it!! Try it out. I will lay odds on you. B."

SubbaRow had immediately after accepting Bell's invitation to join Lederle begun assembling young,

competent men who could be mostly trained in the laboratory itself. So by the time Building 65, a shoe box shaped research laboratory, was ready and SubbaRow came over in May 1940, Malcolm was able to report that “we have the organisation which will be capable of coping with any problems that may present themselves”.

SubbaRow sought in the beginning recommendations from Harvard colleagues and former associates who had taken up jobs in industry. He later sought suggestions from the young, raw PhDs in his department and they would name other bright students they knew in their university. He also made an extensive trip later to the American mid West to visit laboratories and universities not only to study the latest trends in research but recruit men for his laboratory.

Many who came for the interview were surprised that they had to work for a “Hindu”. They found it difficult to understand his highly accented speech but Dr. Merton Lockhart, a deputy of Clark and close friend of SubbaRow ever since he began the Pearl River weekend visits for liver supplies, sat with him and helped improve communications. Once the initial surprise and

language barrier were overcome, they invariably felt they would like working for him. He would assure them that it would be hard work and he would be a hard taskmaster, that they would not get rich but would not starve either, and that they would be starting in a department and a research field for which he saw tremendous growth potential. They could not but help share his dreams and accept his challenge.

SubbaRow succeeded in assembling a remarkable group of young and enthusiastic researchers who came to be known as “Sub’s Boys”. An industrial position at that time helped them to join in the national war effort without being drafted into the Army on assignments in which their training would be wasted. While the original group was formed essentially because of his university contacts and his reputation in university circles, those who came later were attracted by the spreading word that SubbaRow’s department was the ideal set up for research.

SubbaRow was constantly in the laboratories, planning projects, discussing problems and helping solve problems by himself sitting at the bench. He tried to make them share his enthusiasm and ideals and

inspired them by relating their work to that of specialists in related fields who collaborated with them. He would move them with accounts of the particular ailment and the suffering that would be ended by the drugs they were working on.

SubbaRow worked nights and weekends and expected all of them to do likewise.

He didn't want his boys to get married because it interfered with research, one of them alleges. But they all got quickly married with the comfortable salaries he got for them and the protection from Army service he ensured. It became standard procedure for him to tear into them – say how no good they were et cetera et cetera - to straighten them out for a little while after any of them got married or had a baby. Naturally, his reputation was low among the wives.

A new wife arriving in Pearl River went to the beauty parlour and was asked by the operator, "Where does your husband work?" "He works at Lederle," she replied. "Where in Lederle?" "0h, he's in research." "Ah, you're another SubbaRow widow!"

SubbaRow was partly justified in driving his boys so hard. Those protected from the Army service could not

grumble about hard work especially when their contribution was important for the national war effort. In his anxiety to get a fresh view point for breaking through problems specialists got themselves involved in, he would try such unorthodox methods as giving bacteriological work to a biochemist. In such cases he would personally train them to do work for which their academic background did not prepare them.

VITAMINS were then gaining widespread public recognition as essential for improving nutrition and general well being. The rising national appetite for vitamins for medical use and food enrichment and the big government purchases for the armed forces and the Red Cross would swell the profits of drug companies who could meet the growing demand.

Despite his long preoccupation with isolation of vitamins from natural sources, SubbaRow knew that the future was with synthetic preparations. By continuing investigations he had started at Harvard and initiating new ones, he would make his laboratory a leader in the field of nutrition. But Lederle was entering the field years behind its competitors who were well

protected with patents on synthetic thiamine, riboflavin, pyridoxine and pantothenic acid. Only on nicotinic acid did nobody have any patent rights.

SubbaRow put above everything the development of independent processes for synthesising vitamins. He made this the immediate task of a group of organic chemists headed by Dr. Gustaf Carlson who in the Harvard days had once helped analyse liver fractions and had subsequently worked for a year on synthetics with a rival drug company.

They put their attention mainly on members of the Vitamin B Complex: thiamine ($B_1$), riboflavin ($B_2$), pyridoxine ($B_6$), nicotinic acid, biotin, and pantothenic acid.

Pantothenic acid, then believed wrongly to be the long sought elixir of youth and longevity, was first to test the team's talents and Lederle's resources in a big way. It was a tough battle but Carlson worked out, with two associates, alternatives to patented processes for making the vitamin. After many setbacks and delays a plant went into production making 400 kilos of calcium pantothenate a month.

Pyridoxine, whose deprivation causes convulsions in

infants fed with highly artificial milk formulas and in adults addicted to alcohol or processed foods, was however the first success of the organic chemistry group. The group developed chemicals previously unknown to science and from them built the vitamin in order to win process patents. The Stamford division of Cyanamid wanted to mike pyridoxine with the process but Carlson helped build a pilot plant at Pearl River itself. The Calco division however took over later the job of making the vitamin with this process.

Nicotinic acid, which SubbaRow had narrowly missed identifying as the anti pellagra vitamin, could be made with no patent restrictions, and SubbaRow's group worked out a process for converting it into niacinamide which physicians preferred to prescribe. Despite several ideas supplied by SubbaRow, Calco could not, with the plant it had, make nicotinic acid at competitive prices. And Lederle requirements continued to be met with bulk purchases from competitors.

Thiamine cures beriberi, and SubbaRow worked out a new method for making it inexpensively. This process was however partly covered by a patent owned by a rival company. A chemical concern in New York offered

to lend the services of an employee who had previously worked with the thiamine group of a third company. SubbaRow declined the offer since the New York firm thought it had rights over the ideas of its workers not just over the work done at its expense. He gave up the plan to work out a completely independent thiamine process.

SubbaRow's battle for biotin, another B vitamin, demonstrated how scientific success cannot always be translated into commercial profits. Miss Anne Irene Schivek in his department found that a rich source of the vitamin was the broth in which glucose had been fermented with a fungus for producing fumaric acid. She worked out a method for concentrating biotin from the waste liquids of fumaric acid fermentation. But the complicated process for getting pure biotin from this concentrate did not lend itself to commercial production.

SubbaRow therefore decided to get biotin synthesised. A big task force, assembled by him with Dr. B R Baker as leader, collaborated with a group of Cornell University and developed a vitamin "intermediate". The yields were however too low for them to have

sufficient material for attempting synthesis of the vitamin from the intermediate.

SubbaRow now said, “Let us take a lesson from nature.” The chemists were asked to imitate the diphtheria germ which synthesises its biotin needs from pimelic acid. They succeeded in synthesising biotin from pimelic acid, but the cost accountants said the process was not cheaper than the one used by the rival Merck Company. It also turned out that most human needs are met by biotin synthesised by bacteria in the intestines. The need for taking biotin as a dietary supplement was not established. Lederle did not exploit the process developed with an investment of $200,000.

SubbaRow hesitated to institute synthetic studies on riboflavin, whose deficiency causes lip, mouth and skin sores then common in the United States. Carlson had come to him fresh from riboflavin work at Merck whose patent applications were still pending. Henry Piersma, a bacteriologist, was therefore asked to search for a fungus which ferments riboflavin. He secured it from Nazi-occupied Holland and was able to get 99 mg of riboflavin per litre of broth fermented in flasks. Lederle could make riboflavin in huge fermentation tanks and

created interest among enthusiasts for “all natural” vitamins. Rivals caught up with the process. The price fell from $l.50 to 20 cents a gram and threatened to dip to 10 cents. The riboflavin tanks had to be converted for making a new — and more profitable - vitamin.

With all this work, SubbaRow was able to secure his company an impressive portfolio of patents by the middle of 1944. His company was profitably making calcium pantothenate, not so profitably producing riboflavin and was steadily manufacturing pyridoxine. It was not his fault that Calco could not cut its nicotinic acid costs and produce niacinamide. He could not, on the other hand, make much headway with thiamine. Nor could he make biotin synthesis profitable for his company.

If giants like Merck were not shaken, they certainly began to take note of the Lederle David. But SubbaRow could not get any big intellectual satisfaction with alternative processes for making vitamins which others had synthesised first. He was of course not wholly occupied with the patent battle against established drug firms. Nor had he confined himself wholly to vitamins.

He had been busy also with ANTIBIOTICS drugs, produced by some microbes to kill other microbes.

SubbaRow saw the end of the spectacular age of sulpha drugs when in February 1940 he read about the isolation from a bacterial culture of a "bactericidal material". Rockefeller Institute, where Rene J. Dubos and R. D. Hotchkiss made the discovery, agreed to supply the organism which produced "GRAMICIDIN". This antibiotic cured mice infected with pneumonia but was itself poisonous enough to kill the cured mice. The Dubos Material was however not pure, and SubbaRow thought pure gramicidin may not after all be so poisonous.

Henry Piersma within a fortnight produced the crude material on a large scale, and SubbaRow helped him improve his extraction of gramicidin in better than Rockefeller Institute yields.

Dubos himself and other university investigators now began demanding supplies from SubbaRow. Gramicidin had cured mastitis, an infection of the udder, in cows with just a single injection.

Gramicidin had been made by SubbaRow the first-ever antibiotic to be commercial manufactured and clinically

used and it was in steady production at Pearl River. But not all the requests for supply could be met. SubbaRow planned expansion of the gramicidin facility, but a report now came from an agriculture experimental station saying the preparation caused tissue damage in the udder of treated cows. He therefore stopped production, convinced gramicidin had no future.

Even before his disenchantment with gramicidin, SubbaRow had turned his attention to PENICILLIN, the antibiotic with miraculous powers against a wide range of diseases including pneumonia.

He learnt in September 1940 how Ernst B. Chain, the Oxford biochemist, had been able to obtain penicillin, discovered 12 years earlier by Alexander Fleming, in "a considerable yield" and how Howard W. Florey of the Dunn School of Pathology had found it to have remarkable activity against the gas gangrene microbe among other killer germs.

SubbaRow secured the penicillin producing fungus, ***Penicilium notatum***, with the help of Charles Thom, the American mycologist, to whom the British had sent it in 1930 for identification. By December, he had Piersma

growing the fungus in different media to find out which one was best for getting maximum yields of penicillin. By adding digested milk protein, instead of yeast extract, to the original mineral glucose medium, Piersma could obtain 20 units of penicillin compared to the two units reported by the Oxford scientists.

The Oxford and the Pearl River teams had an unexpected meeting on July 31, 1941 at the Northern Regional Research Laboratories in Peoria. Florey and his colleague, N. H. Heatley, had arrived in the United States the previous month after failing to interest British drug houses in making efforts to increase penicillin output. They had been referred to Peoria mycologists who had experience growing ***Penicilium chrysogenum***, closely related to the Penicillin organism, in a medium for large-scale production of a textile reagent. SubbaRow and Piersma were in Peoria to meet the same mycologists.

The Oxford scientists found SubbaRow's penicillin to be purer than theirs. Because it was pure penicillin, it retained activity only for a few days unlike the sodium salt of penicillin used by the Oxford Group.

Florey and Heatley were impressed enough to visit Pearl

River on September 9 “to discuss the possibility of getting penicillin made in large quantities”. SubbaRow was away with a “cold” but Malcolm gave them another supply of penicillin, which was more potent than any reported by others. It was agreed that SubbaRow would attend a meeting Florey and Heatley were organising under the auspices of U.S. Government’s Committee on Medical Research for getting the cooperation of American drug houses to produce penicillin.

Either because of over confidence in SubbaRow or due to suspicion of “creeping socialism”, Bell wished to keep Lederle out of Anglo-American drug house collaboration under government auspices for producing penicillin by fermentation and synthetic processes.

SubbaRow and his scientists, working independently, could make no significant progress in chemical synthesis. Nor could they solve the problems of producing penicillin in big fermentation tanks. Lederle had to suffer the humiliation of getting the War Production Board assignment for producing penicillin in bottles which is less productive and more cumbersome than tank production assigned to competitors. SubbaRow’s men accumulated enough

know how by the time the War ended and helped Lederle build a deep tank plant capable of producing 1.5 million vials of penicillin a month.

BY THEN, SubbaRow's department was busy with promising new antibiotics it was getting from a big programme to screen soil and other samples it was getting from everywhere.

SubbaRow had organised his department like an institute for nutritional and antibiotic research. Here were biochemists to isolate nutritional factors from natural substances, microbiologists and animal nutritionists to evaluate them, pharmacologists to study their effect on body functions, and organic chemists to synthesise what proved to be vitamins valuable in human nutrition. Here also were biochemists, bacteriologists, biologists, pharmacologists and organic chemists isolating active antibiotic material from various sources, testing their action on microbes and animals, assessing their toxicity and attempting synthesis if natural yields were insufficient for large-scale production.

And he, SubbaRow, moved among all of them

animating their diverse talents and directing them toward the conquest of nutritional deficiencies and infectious diseases. His inspiring words how valuable their work was for alleviation of the suffering humanity served to motivate them all.

Research was simultaneously progressing on both vitamins and antibiotics. More than one vitamin and more than one antibiotic were on the programme all the time. SubbaRow directed the scientists like a maestro who divides his time conducting several orchestras which played not just one kind of music but the whole range from classical symphonies to jazz improvisations. He tackled research problems like a chess master pitted against several opponents at the same time. It was for this opportunity after all that he had forsaken the academic world at Harvard.

At Lederle, SubbaRow was in the beginning only one in a committee which ruled on research. But Ralph Wyckoff left Pearl River in 1942 when his horse sleeping sickness vaccine was so successful in controlling the disease in the Americas that vaccine production had to be stopped and half a million dollars in returned vaccine written off. And Joyner joined the

Army Medical Corps, resenting SubbaRow building up his own group of bacteriologists as the antibiotic programme expanded. The viral and bacteriological research departments came under SubbaRow who was promoted "Director of Research" on October 1, 1942.

SubbaRow assumed full responsibility for medical investigation by doctors and hospitals of the products of his research. Changes in Lederle Laboratory management left him sole responsibility for administering his department. He had to go to Malcolm or Bell now only for funds.

He steadily recruited a large number of new scientists and technicians to meet the specific needs of his changing research objectives. Luckily in a shake up that nobody planned in the second half of 1943 practically the whole of his original team left Lederle. He might otherwise have had a problem integrating old members with newcomers. Still he was sad to see the departure of many who had given their best and helped him prove himself by slaving in a way the newcomers would never have to.

The search for the backdoors of the vitamin mansion was over.

Competition to secure a position on products over which his organisation would have no exclusive rights more or less ended. His laboratory was now at the vanguard of vitamin and antibiotic research. Each coming New Year would see the unveiling of a new drug, the conquest of a previously defiant disease.

# The Looking Glass War against Mirror-Image Maladies:

## Folics against Anaemia and Anti-folics against Leukaemia

SubbaRow had left Harvard for Lederle in the hope of bettering the chances for his isolating that elusive factor in liver that would conquer not only pernicious anaemia but tropical sprue which had taken him to the jaws of death and carried away brother Purushottam.

The original idea that both pernicious anaemia and tropical sprue were variants of the same nutritional deficiency and could be cured by the same vitamin had long since been challenged by a study among expectant mothers in Bombay. There, Dr. Lucy Wills and Dr. Manek M Mehta of the Haffkine Institute found that the anaemic poor women had a sound digestive system and that tropical sprue manifested among them when pregnancy or illness increased the demand for an unidentified food factor their blood needed. This was in contrast to Boston's pernicious anaemia patients whose degenerate stomach walls could not absorb the blood-building factor present in their rich food. When Dr. Wills later reported that sprue

in monkeys was cured not by APAF-rich liver concentrates but by the cruder liver extracts, SubbaRow had even in 1937 turned his attention to the liver plant wastes.

Then a sprue patient of Dr. Jacobson got better with an APAF-rich liver extract. Instead of casting doubts on Lucy Wills's claims, SubbaRow decided to test every liver fraction in both pernicious anaemia and tropical sprue patients. Since sprue is not common in the United States, he set up the sprue investigation programme in Puerto Rico with Dr. Ramon M Suarez in Hospital Mimiya at Santurce.

SubbaRow's liver men at Pearl River were put to work on the first liver extract Suarez reported beneficial. They kept concentrating the 'sprue factor' along the lines encouraged by reports flowing in from Santurce only to find at the end of two years that their material contained mostly of the already identified vitamins of the B Complex. The 'sprue factor' had been lost somewhere while being concentrated.

As luck would have it, a liver fraction SubbaRow was also testing as a chicken growth promotion factor turned out at this time to be the true sprue factor. SubbaRow brought over to Pearl River in October 1941 the man who had

originally traced the 'chick growth factor' in yeast. With the arrival of Dr. E L R Stokstad from Petaluma in California, SubbaRow got the last element for success. He could buy unlimited quantities of liver and yeast, and his pilot plants could process a thousand pounds of them at a time. And the concentration of the factor could be followed with two microbes which also thrived on it. And he himself with his unrivalled knowledge of fractionation techniques and organic procedures could guide Stokstad who was eager to succeed and young enough not to have any fixed notions about the path to success.

SubbaRow started Stokstad on a tar-like waste from the liver plant. Each milligram of it had 20 units of the chick growth factor. Stokstad's task was merely to concentrate the active material just 50,000 fold!

Stokstad easily removed a mass of inert material from liver tar and ran the extract up a glass column filled with activated clay and the active material separated out in a distinct colour zone on the column. On extraction with alcoholic ammonia, it was found to have 340 units of the growth factor per milligram -- a 17-fold concentration. This was the new technique of chromatography, an improvement on charcoal adsorption SubbaRow had used

in his Harvard work on APAF.

SubbaRow's appreciation of organic chemistry techniques now came into play. If the factor, by now called folic acid, could be converted into its ester or alcoholic salt, the oily substance would separate out while the impurities remain dissolved in water. Since direct esterification of folic acid was not possible, they converted it into its barium salt. The ester then obtained had a potency of 3450 units. In three further steps, Stokstad raised the potency from 3450 to 370,000 to 660,000 to 1,030,000 units. He converted the methyl ester back to free folic acid on April 5, 1943.

It had taken Stokstad 21 months and Lederle had spent 100,000 dollars on the effort. But the folic acid yield from liver was too low for it to be of any practical value. A thousand pounds of pork liver costing 255 dollars gave 60 mg of folic acid, hardly the size of a pea and no more than three days' requirement of a normal adult.

SubbaRow decided to scrap the project. He had found a richer source of folic acid!

Late one afternoon a year earlier in June 1942 SubbaRow was walking down to the laboratory with Henry Piersma carrying a desk-drawer full of flasks with cultures of a riboflavin-producing microbe. It was either SubbaRow

or Piersma who pointed out one of the flasks and exclaimed: 'Isn't it amazing how much riboflavin this organism produces?' It was just fantastic. The other said, 'I wonder if this organism produces any other vitamin.' The first replied, 'Perhaps I should take a sample of this culture medium and let Al Dornbush run an assay.'

SubbaRow was waiting the next morning at the laboratory and told Piersma, 'Imagine, that sample is full of folic acid.' A contaminant in that particular culture was obviously producing folic acid. Luck was again favouring the prepared mind. But hard luck! The contaminant could not be isolated as Piersma had sterilised the flask after taking out the sample for Dornbush.

SubbaRow asked Dr. Brian Hutchings, a Wisconsin biochemist he had hired because of his previous work on folic acid, to capture the contaminant from bottles and tanks in Building 62 where riboflavin was being fermented.

Hutchings exposed Petri plates smeared with yeast extract and glucose in the building and incubated them for 24 to 48 hours. Of the several bacterial colonies that developed one was a medium-length rod. And, presto! This benign cousin of the diphtheria germ produced folic acid!!

Hutchings developed a simple medium in which the bacterium grew quickly and from which folic acid could be easily harvested. Fermentation experts grew it in 200 gallon tanks and fermented large batches of broth. Hutchings used Stokstad's methods to isolate folic acid from the broth but crystallisation defied him. SubbaRow put on the job Nestor Bohonos, a biochemist taken off another project, and he got the crystals within days.

Microbial yields were big compared to liver yields but SubbaRow, even as he ordered scaling up the job to manufacture, decided not to depend entirely on fermentation broths. He decided in August 1943 to use crystalline folic acid from Hutchings's laboratory to attempt synthesis of the vitamin. It was a wise decision. A year later the pilot plant was still beset with problems the technicians could not tackle. SubbaRow took the technical problems upon himself, put 20 people on investigating fermentation in all its phases, and provided pilot plant people with data to get over the difficulties. They were soon producing 15 grams of folic acid a week at an average cost of $200 a gram. Large tanks using cheaper ingredients for fermentation were set up with hopes of bringing down costs to four dollars a gram but

new snags arose. Although these too were overcome, SubbaRow wound up the operation on April 28, 1945! His organic chemists had synthesised folic acid!!

But it had been touch and go. Shortly after SubbaRow initiated synthetic studies in August 1943, Gustaf Carlson, his chief organic chemist, left Pearl River. Neither getting a replacement nor accepting a suggestion to bring in Vincent du Vigneaud of biotin fame as consultant, SubbaRow decided to directly supervise folic synthesis. Initially he did not even deploy organic chemists. Biochemists Stokstad and Hutchings broke the folic molecule and found two of its constituents: glutamic acid from which gluten the wheat protein is built up and a fluorescent pigment akin to xanthopterin the yellow colour of butterfly wings. When the pigment, the 'pteridine' nucleus of the molecule, defied identification, SubbaRow brought in the organic chemists, John Mowat and Jim Boothe. The mystery only deepened when they broke the folic molecule different ways and got two different pteridines and speculated about the presence of two pteridine nuclei in the molecule. They however found in the non-pteridine part of the molecule not only glutamic acid but para-amino-benzoic acid (PABG) a member of

Vitamin B Complex, and figured out the linkage of the two in the folic molecule. When they too could get no clue as to the identity of the pteridine, the synthesis itself providing a clear picture of the vitamin molecule began to be considered.

PABG and Triamine (TA) used in the synthesis of xanthopterin were obviously the chemicals to start with. The chemical had to be chosen that would react with TA to complete the pteridine nucleus, take on PABG at the right place and provide the speculated 'fourth carbon fragment'.

On Monday the third of July 1944, Mowat brought to the lab his weekend notebook and got it authenticated for several ideas including di-bromo-propion-aldehyde as the third chemical. Later in the day he entrusted the job of preparing the aldehyde and attempting synthesis to Coy W. Waller who had just been hired by SubbaRow from the University of Minnesota.

Waller prepared the aldehyde, reacted it with TA, condensed the product with PABG and got a brown mud. He asked for and got the permission to try it all over again substituting the aldehyde with mucobromic acid which too had two bromium atoms but with an extra carbon that

could provide the mysterious fourth carbon of the folic acid. When he did it the customary stepwise fashion, the mucobromic and PABG formed a glutamate that would not readily go into reaction with TA. To force the reaction, he put the mixture on a Friday evening in a 'sealed bomb', deciding to keep it cooking for 72 hours.

Waller went Sunday afternoon with some friends including Beverly Braun, who would later become his wife, on bicycle riding. During dinner at end of the picnic, he felt anxious about the Bomb and announced he would go back to the lab to make sure the reaction wouldn't go too far. Miss Braun went with him, saying she would start some new cultures for next day's job in the bacteriology lab where she worked. Whom did they come face to face at Waller's lab but SubbaRow who was there also to see everything went well. The straight-laced director called Waller away and Beverly Braun, standing anxiously in the lab, could hear him speak crossly.

The 'sealed bomb' was no success but by changing the reaction steps, Waller got 0.1% folic activity. His hopes roused, he asked himself, could it be that during the mucobromic-PABG reaction a compound was formed that would, if it got no time to decompose, react with TA and

form folic acid. He went to SubbaRow and asked if he could throw all the three chemicals together and allow them to cook in the same soup. The procedure would be unorthodox but SubbaRow took a look at the persevering chemist and said, 'Coy, try anything. Just get it.'

Waller cooked all the three together in a kettle and got 'a black, crude and gawky stuff'. He was too fastidious to send that for assay. It might have remained on the shelf like the brown mud had not SubbaRow walked in and said, 'Why not run a bioassay on this stuff?' The analysts said the stuff had 'one percent activity—may be two per cent or so'.

But mucobromic acid was not a satisfactory reagent and a four-carbon compound like it was not needed as carbon dioxide escaped during the reaction proving there was after all no fourth carbon in folic acid. It occurred to Waller to resurrect the brown mud lying on the shelf since July and have it assayed. It had 0.75% activity! Waller now got hold of the original three-carbon aldehyde proposed by Mowat and threw it along with PABG and TA in his 'shotgun' reaction. What he now got had 15% activity and a subsequent batch showed 20% activity.

Mowat phoned the good news to Bound Brook where the

chemists of Calco, sister division of Cyanamid, were following the work at Pearl River so they could take up process development and production the moment research was completed.

Major chemical activity shifted to Bound Brook. Within a week, the Calco chemists prepared the first 'laboratory' batch of 1.7 grams of 15% pure folic acid. The first pilot plant batch of 4763 grams of folic acid was ready on July 6. This was 997 grams of 'real' folic acid. The entire Pearl River group drove over in SubbaRow's car to get 'a kilo of folic acid all in one bottle'. Regular manufacture began on September 26, the first batch yielding 14 kilograms of 'real' folic acid. Twelve kilos were shipped to Pearl River on December 15.

The chemical synthesised in spring was on the manufacturing line in fall. A gram of ***synthetic*** folic acid cost $8.70 compared to $123 for ***fermentation*** folic acid and $4250 for ***liver*** folic acid.

A joyous Bell was impatient to announce the synthesis in March itself but was restrained by patent attorneys to wait until July 18. That day he sent a telegram to the annual conference of the American Association for the Advancement of

Science (AAAS) offering research workers limited supplies for investigating its vitamin properties.

When they were permitted to disclose minimum scientific data in professional journals, Sub's 'Boys' discussed the paper among themselves and decided to list all the sixteen who had contributed, at Pearl River and at Bound Brook, to the success in the alphabetical order of their names. The Boys thought SubbaRow had been no mere supervisor to have his name put in the last but was one whose contribution had been 'as much as, perhaps more than anyone else's'. In the Pearl River listing, SubbaRow's name appeared just above Waller's when the paper was published in the August 31, 1945 issue of ***Science*** the journal of the AAAS. SubbaRow took little interest in all this. He was preoccupied with the question, 'What value is folic acid?'

There was any number of volunteers to provide the answer. Among them were Tom Spies the old fighter against 'starvation sickness' as he called the nutritional deficiency disorders and William J. Darby of Vanderbilt University School of Medicine at Nashville, Tennessee.

Spies was amazed when five pernicious anaemia patients showed an upsurge of well being within four days and

practically a normal blood picture by the eighth day.

Darby reported the effectiveness of folic acid against sprue, the old enemy of SubbaRow: A 51-year-old patient with a ten-month history of sore mouth, diarrhoea, weakness and weight loss responded spectacularly. Mouth sores disappeared on the fourth day, the blood picture was normal on the ninth day and the appetite was excessive. The man was in excellent health when he came three months later for a check up. Equally impressive was the response of other patients.

Spies now took folic acid to Puerto Rico for extensive trial in sprue among the patients of the Ramon Suarezes, father and son. He went on to Havana, Cuba, and set up a trial at General Calixto Garcia Hospital. He gave folic acid in all to 218 anaemic patients in the course of a year and hailed it as the fourth element in his mixed vitamin therapy for starvation sickness.

Despite the confirmation by other doctors of the initial finding of Spies in pernicious anaemia, SubbaRow was far from convinced that folic acid was the long-sought APAF. The highly purified anti pernicious anaemia fractions of liver showed no chemical resemblance to folic acid. SubbaRow on the other hand had no grounds to

discourage physicians who were resorting more and more to folic acid in pernicious anaemia since patients develop sensitivity after a while to liver injections. This led to a totally unexpected consequence. An increasing number of relapses and severe progress of nerve disorders among the patients soon came to be reported. The ***New England Journal of Medicine*** issued in November 1947 an editorial warning against the use of folic acid not only in pernicious anaemia but in sprue.

Careful studies however established that folic acid, which is present in the blood and tissues of all normal individuals, has no bad effect on the nervous system. Folic acid cures the blood disorder in pernicious anaemia but has no effect on the associated nervous disorder which runs its course. It not only cures sprue but has caused no nerve damage among the countless millions it has cured of sprue and other forms of anaemia. With folic acid, SubbaRow really avenged the death of Purushottam!

* * *

Folic acid trials confirmed that pernicious anaemia with the nerve changes it brings about is quite distinct from sprue and other ***megaloblastic*** anaemias.

Although he had neglected it after moving to Pearl River,

SubbaRow had not altogether abandoned his search for APAF in liver. He always had someone working on liver specifically to try out his ideas on APAF. He did not know it but he had in fact obtained what was probably his richest APAF fraction within months of shifting to Lederle Laboratories. Set by him to employ the best of classic liver fractionation techniques, Frank Ablondi had got a beautiful pink solution. Pink is also the colour of Reinecke Salt, a toxic chromium compound, used to precipitate the inactive material. SubbaRow was astonished the colour remained despite his having broken down Reinecke Salt with silver nitrate after it had served its purpose. Believing that all traces of the poisonous salt had not been removed, he had the solution extracted with methyl alcohol. Along with the colour most of the activity got washed out.

SubbaRow tightened procedures to ensure removal of Reinecke Salt but Ablondi still got a pink solution. He shook his head and said reproachfully, 'Frank, you didn't get the Reinecke out.'

Nestor Bohonos replaced Ablondi but try as he did he just could not get active fractions which were not pink. Otto Weiland replaced Bohonos on the sole task of obtaining an active liver fraction that wouldn't be pink.

Weiland cried desperately after a year, 'Why use Reinecke salt at all if it is so risky?' SubbaRow abandoned it in favour of metallic sulphates. Weiland ran the resulting solution up the chromatograph. The ***pink*** fraction on the column boosted blood formation in chicks. Not trusting the animal test and unable to get over his colour fixation, SubbaRow did not allow the pink substance to be given to pernicious anaemia patients.

After it was finally shown that folic acid was not APAF, SubbaRow was willing toward the end of 1947 to face the fact that pink and APAF activity went together. He was ready to lift the ban on its clinical testing.

The opportunity to test came on Christmas Eve when Spies cabled from Cuba that he had a pernicious anaemia patient. Not finding Weiland anywhere, SubbaRow waited at his house until six in the evening when the isolationist returned happily, his arms full of Christmas gifts. The festivities at home spoiled, Weiland went to the laboratory and rushed to La Guardia airfield in New York City to fly out the pink fraction to Spies. The 65-year-old Cuban patient, admitted in hospital in a confused state of mind, recovered fast. Weiland forgave SubbaRow on learning that 30 drops of his Christmas Eve preparation gave back

the Cuban his appetite on the second day, enabled him to walk on the 25th day and made him soon well enough to go home.

When on April 2, 1948 came a similar glowing report about one c.c. of the same 'special liver fraction' administered to a woman patient in Alabama, Weiland was glad his troubles with SubbaRow — working nights, weekends and holidays — would soon end.

What ended was SubbaRow's long search for APAF on April 16. That day's issue of ***Science*** carried a Merck Research Laboratories' claim that it had isolated from liver a crystalline compound which in ***micro***grams induced positive blood response in pernicious anaemia patients. It later turned out that Merck got this Vitamin $B_{12}$ not from liver — although it was technically possible to get it so as an expensive curiosity — but from fermentation broths of the antibiotic grissin aided by a microbiological assay acquired quite fortuitously.

Although Vitamin $B_{12}$ is without doubt the APAF, it was folic acid in liver that cured the patients of George Minot and William Murphy and set in motion the search for the pernicious anaemia cure. Those unhappy patients with degenerate stomachs could not have assimilated the 0.06

mg of $B_{12}$ in the half pound of raw beef liver they were daily fed.

SubbaRow in his success in getting out that original Minot-Murphy talisman and showing it was not the real pernicious anaemia cure had roused fresh interest in APAF not only in himself but in other vitamin hunters. His pioneering fractionation work and his finding that fermentation broths are good vitamin sources inspired those who placed 'the last stone and stepped across the *terra firma* of accomplished discovery'.

* * *

Pernicious Anaemia and sprue cures are not the only disease fighting weapons to emerge from the confusion caused by folic acid and resolved with its prodding the isolation of $B_{12}$. It also led to an entirely new line of fighting cancer with chemical agents, thanks to SubbaRow's ever probing, forever analytical mind.

SubbaRow had a report from an investigator that folic acid obtained from fermentation broths had to be digested with hydrochloric acid to make it as active as folic acid in promoting the growth of a certain microbe. The two folic acids were indeed different. An analysis showed that ***fermentation*** folic acid has three molecules of glutamic

acid whereas ***liver*** folic acid has only one glutamic molecule. In mice, fermentation folic acid stopped and even eliminated cancer cells and liver folic acid, on the other hand, promoted the growth of cancer cells. Cancer workers began to clamour for fermentation folic acid and Jim Boothe synthesised it early in 1947.

SubbaRow not only supplied this three glutamic folic acid or ***teropterin*** to Lewisohn but established a full evaluation programme with his old friend Sidney Farber at Boston's Children Hospital. In cooperation with other Boston hospitals, Farber administered teropterin to cancer patients for whom no known treatment offered any hope of cure.

Improvement observed in many of the first group of Boston's 90 patients was neither constant nor lasting but it occurred frequently enough to encourage further study. Particularly remarkable was the great sense of wellbeing the patients felt. They appeared to be more energetic, ate better, showed less irritability and fear of death, suffered less from pain, and needed less of drugs to alleviate pain or sleep.

And Lewisohn reported the remarkable prolongation of life and considerable easing of pain of Babe Ruth. The

celebrated baseball player had entered hospital with his cancer spread despite surgery and radiation treatment. He was in terrific pain, could not sleep, could not eat solid food and could hardly talk. With daily injections of teropterin, the tumour in his neck shrivelled in less than six weeks. Ruth had hardly any pain. He could eat solid food, sleep, talk better and gained 12 pounds. Although he was not cured, Ruth's case roused considerable interest in professional circles.

A thorough investigation of teropterin following insistent demand for it from clinics throughout the world showed it was at best a palliative. The temporary shrivelling of tumours reported by Lewisohn and Farber has never been satisfactorily explained. Teropterin was withdrawn as a cancer drug but it served the cause of cancer fight well by drawing attention to folic acid derivatives.

SubbaRow was set to thinking when Farber later reported that teropterin accentuated the leukaemic process in children. Since teropterin is a folic acid ***analogue***, he reasoned that folic acid ***antagonists*** - folic acid derivatives which reversed the vitamin effects of folic acid - might inhibit leucopoiesis (white blood cell formation). X-methyl folic acid, the first antagonist his chemists synthesised,

caused in rats a destruction of blood cells that could be stopped with vitamin folic acid.

Folic acid antagonists were thus indicated in leukaemia to check the increase in the number of cellular elements in the patient's blood especially when vitamin folic acid could keep the action of the antagonists within bounds.

SubbaRow got his chemists to make all possible chemical compounds closely resembling folic acid and had them tested for their vitamin or antivitamin properties. And, he took two of them to Farber in Boston. Neither saved the 21 children treated for leukaemia but postmortem examination of their bone marrow showed an improvement in the formation of blood. The doctors felt justified in asking SubbaRow for a 'more powerful anti-folic'.

The Boston ***Herald*** on April 9, 1948 carried pictures of two boys saved by ***aminopterin***, the 'powerful anti-folic synthesised by SubbaRow's chemists. Robert Sandler, one of the boys, was shown with Elliot, his identical twin. It was

difficult to make out from the picture that Robert had only recently escaped from the jaws of leukaemia whereas Elliot had never suffered a day of sickness in all his three years. Robert and George Jason, a four-year-old also featured in the newspaper story, were among the ten who had responded favourably in a group of 16 leukaemic children to whom aminopterin was administered by Farber and associates.

Doctors used to resign themselves to the death of children from leukaemia in days or weeks, six months at best. They were now impressed that among the Boston Ten was a child alive 20 months after leukaemia was diagnosed and that aminopterin had effected repeated remissions -- temporary return of the white blood cell count to its normal range. Previously no child with leukaemia had shown two remissions.

Boston ***American*** came out the next day with the report that SubbaRow whose chemical research had yielded the miracle drug was 'a Hindu' who had previously worked at Harvard Medical School.

Although all patients, despite remissions sometimes lasting four months, suffered relapses and any further administration of aminopterin was futile, it was an

accomplishment against a disease whose treatment was so long associated with despair. The margin was also slim between the effective aminopterin dose and the dose that caused blood changes uncontrollable by vitamin folic acid.

Farber asked SubbaRow for a less toxic but more powerful anti-folic. SubbaRow set his chemists the task of synthesising a chemical that was as harmless as teropterin but as active as aminopterin.

METHOTREXATE which is one-fifth as toxic as aminopterin but requires a fivefold higher dose is now the preferred drug. It allows physicians to better adjust the dosage. Used in combination with other drugs, it has prolonged the lives of children with acute leukaemia for as long as five years. This is considered by doctors to be virtual cures, considering how fast the children used to die previously. Once remissions are achieved, many children feel well and enjoy life. There is always the hope that a permanent cure will be discovered during the extended lease on life.

Late in 1947 the conquest of cancer became the 'magnificent obsession' of SubbaRow. He established at Pearl River

the first cancer research unit in any American pharmaceutical company and supervised closely a screening programme. He wanted to set up a new cancer research laboratory at nearby Wyckoff but died soon after the building plans were approved. His colleagues believed he would have conquered cancer had he lived another ten years.

Chemotherapy of cancer or treatment with drugs remains the main hope for the eventual conquest of cancer. It owes a lot to SubbaRow who switched to folic antagonists despite initial reports crediting folic analogues with anticancer properties. SubbaRow relied on observation rather than theory.

George Hitchings, a Harvard colleague of SubbaRow's, in independent research, discovered in 1951 that purine antagonists supplement folic antagonists in the chemotherapy of leukaemia. He lived to receive the Nobel Prize 37 years later in 1988. SubbaRow would presumably have shared it had Nobel permitted posthumous awards.

# The Rescue from the Ugliest Disease

The Second World War made the United States Army get interested in drugs to treat diseases the American soldiers would be exposed to in the tropics.

This was opportunity for SubbaRow to conduct in the United States research to fight filariasis and other tropical diseases he had seen causing great suffering among people in India.

It was however only in the spring of 1944 that he could organise a "parasitology" group at Pearl River. He brought Dr. Redginal Irving Hewitt doing research on bird malaria in Alabama and set him screen chemical and other material for their effectiveness in ducklings infected with experimental malaria.

Within five months SubbaRow talked Hewitt into switching research from malaria to filariasis. Filariasis is the underlying illness in what manifests itself as elephantiasis or the ugly swelling of legs. SubbaRow had seen the agony and shame of the sufferers and had conducted some research into the disease at the Ayurvedic College in Madras.

In the United States, only the isolated community of Charleston, South Carolina, was troubled by filariasis but Hewitt was soon as enthusiastic as SubbaRow in finding a cure for soldiers returning home from the Pacific with the dreaded disease.

The young filarial larva discharged by the mother into the blood stream usually causes no complications. The real trouble starts when it is sucked by a mosquito in whose body it matures and is subsequently discharged into a man or woman by the mosquito. It now makes for the lymph ducts in large numbers, concentrating particularly in the lymph glands. Lymph fluid, thus blocked, flows into connective tissue and causes it to grow in size. The skin in affected parts thickens. There is muscular pain and fever.

Dogs infected with the heart worm, which is related to the parasite in man, were till then used for screening compounds against filariasis. But they were too expensive, required large amounts of test chemicals and had to be returned to owners after treatment. Luckily, they learnt that large percentage of cotton rats in the Florida wilds is already infected with a filarial parasite. They started with a screening programme that required

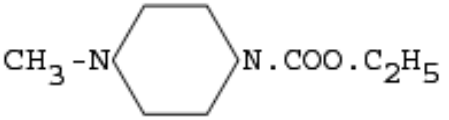
20 to 40 cotton rats a week and soon needed a weekly supply of 200.

SubbaRow sent Hewitt any and every chemical he came across — organic eyes, sulphonamides, quinolines, sulphones, cyanamides and piperazines. Five hundred and seventeen chemicals went through the cotton rat screen before Hewitt found what SubbaRow wanted.

In April 1945, six months after the screening began, Hewitt found the compound code numbered "180 C" somewhat reduced the filarial larva count in the blood of a cotton rat. It was not a dramatic reduction but Hewitt decided to test the chemical again in a number of cotton rats. 180 C was a chemical synthesised by a Calco chemist as a possible analgesic and had been sent over to Hewitt because its pain killing power was negligible. Hewitt went wild with excitement when the repeat tests showed that 180 C, whether injected or given by mouth, caused a rapid reduction in microfilaria or young worms in blood. But 180 C had very little effect on the adult worm.

SubbaRow had chemists both at Pearl River and Bound Brook synthesise a number of piperazines to which group of chemicals 180 C belongs. Since the parent

piperazine, once used in gout, was inactive in the rats, the anti-filarial activity did not lie in the piperazine nucleus but either in the "methyl" or "carbethoxy" side-chain of 180 C:

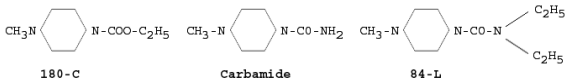



Methyl Nucleus Carbethoxy

It was theoretically possible to make 256 different piperazines by substituting the side chains with other alkyl (alcohol) groups, since piperazines with which the carbethoxy side-chain were more filaricidal than those which did not have it, a whole series of compounds were prepared substituting the “methyl” side-chain with other “alkyl’’ groups. None of the 35 piperazines so prepared was better than 180-C.

The chemists therefore turned to the carbethoxy chain and prepared a number of acid derivatives. The anti filarial activity shown by a compound related to the carbamic acid ($HO.CO.NH_2$) derivative encouraged SubbaRow to get all possible chemicals related to this “carbamine” synthesised.

A compound, 84-L, made by substituting the two end hydrogen atoms with ethyl ($C_2H_5$) groups was unmatched in its anti filarial activity:




180-C Carbamide 84-L

Diethyl carbamyl 4 methyl piperazine — to spell out the chemical name of 84-L synthesised by Dr. Sam Kushner in SubbaRow’s group of organic chemists at Pearl River — immobilised filarial worms in rats, dogs

and frogs in a dramatic fashion. A larva dropped into a test tube full of the chemical would contract in spasms, its whip would contract into a tight coil within five to fifteen minutes and then straighten out to remain completely motionless.

Hewitt tried various doses and treatment times in 212 cotton rats and 25 dogs. Adult worms in cotton rats succumbed with oral treatment of several weeks. Dog owners exasperated Hewitt by demanding the return of their pets after treatment. But in a few dogs he could sacrifice, the hearts were free of worms. The worms were found dead in the blood vessels of the lungs.

84-L was tested in animals by pharmacologists and found to have low toxicity. It was moreover rapidly excreted by kidneys and hence posed little danger of accumulating in the body in toxic concentrations. Hewitt and his colleagues swallowed 84-L in high doses and suffered only a little nausea.

SubbaRow sent Hewitt and Kushner to Puerto Rico to personally deliver 84-L to Dr. Jose Oliver Gonzales of San Juan's School of Tropical Medicine, and then have a three week holiday in that Caribbean island.

Dr. Gonzales and Dr. Santiago-Stevenson, his colleague,

administered 84-L to 26 Puerto Ricans and reported that it caused rapid disappearance of microfilariae from the blood stream, possibly acted on the adult worm as well and caused no serious side effects.

Hewitt took Hetrazan, as the drug was now named, to all parts of the world. In St. Croix, one of the Virgin Islands where generations have suffered from filariasis, he initiated in 1951 a programme in which the drug was given virtually to the whole population. Some 85 per cent of those treated were found free of microfilariae when a check was made a year later.

Hetrazan received its most extensive trial between 1955 and 1959 when six million people in twelve states of India were given the full five-day course. A committee of the Indian Council of Medical Research ruled against mass programme with Hetrazan as it causes unpleasant, although transitory, reactions from nausea and stomach upset to body-ache and fever. These reactions result from the sudden release of protein when microfilariae are

killed effectively within such a short time. It has therefore to be used under medical supervision and is positively beneficial in early diagnosed cases of Filariasis, the ICMR ruled.

Although it certainly is less toxic than heavy metallic drugs and dyes previously used in the treatment of the disease, there was therefore hesitation for many years, in employing diethylcarbamazine (DEC), the generic name for Hetrazan, in mass campaigns against the scourge of elephantiasis. A few years ago, WHO the World Health Organisation found that the side effects were due to unnecessarily high dosages prescribed and that it was enough to administer only a single dose of DEC, concurrently with ivermectin, to keep blood free of filarial worms for a whole year. And WHO has since then made DEC a key element of its worldwide campaign for the elimination of elephantiasis.

# Polio Defies SubbaRow

The 1946 polio epidemic in the United States, the second worst recorded till then, set SubbaRow to brood about yet another of the unfinished businesses of medicine – the conquest of viruses.

Although some 90 per cent of those who catch the infection do not suffer anything more serious than mild fever, headache and general malaise, polio's crippling effect in the rest is too tragic for words. Some 25 per cent of those who develop symptoms of paralysis suffer severe permanent disability and another 25 per cent have mild disabilities. Some die of respiratory failure. SubbaRow wanted to organise a screening programme but could not interest Dr. Harold Cox, heading his virus research section, in any programme to control the polio virus with drugs. He therefore created a new virus group under his direct control.

He decided to test chemicals, dyes, botanicals, sulphas and any of the scores of other agents in mice infected with the virus of the horse sleeping sickness. Like the polio virus, this one attacks the nerve tissue and causes

inflammation of the brain and the spinal cord. Millions of mice would be needed and SubbaRow found in Fritz Popken, a friendly, 38 year-old German, the ideal man able temperamentally to stand the monotony of it week after week. Popken and Miss Kathleen Richards, his assistant, proved equal to the challenge of giving 32,000 injections a day and keeping records on every mouse. SubbaRow had assembled 40 drugs before the two started. Each of them had to be tested in 20 mice. With the deadly virus brew shot into the belly, half of each group of animals were allowed to get sicker each day, become paralysed and die on the fifth or sixth day. The other ten got the test drug in four injections a day after the virus had a head start of 48 hours.

Popken and Richards had for eight weeks nothing but to report death of the mice -- those who got the drugs as well as those who did not. Then in June three mice in a group that got a chemical sent by Calco Laboratories at Bound Brook survived with no signs of paralysis!

Martin E. Hultquist, who had prepared the chemical that saved the three mice in Popken's animal house, immediately began tinkering with the chemical molecule. With five other chemists assisting him, he

began turning out a series of related phenol-sulphonamides.

Three months later Popken got Sulpha No. 261 — phenol sulphonamide with a thiazole molecule hooked to its nitrogen – and it saved five out of ten mice in the very first test group. With larger doses, the score went up to three saved out of four. This was the first time *any* drug had been demonstrated to have *any* really marked activity against *any* virus. Viruses were after all not immune to chemotherapy.

Would pheno sulphazole be able to attack the polio virus in an equally remarkable fashion?

SubbaRow established collaboration with Dr. Murray Sanders at the Columbia College of Physicians and Surgeons. Sanders had nearly ten years of research background in isolation and cultivation of viruses including a monkey polio virus which could induce paralysis in mice. He had also a small Rhesus monkey colony where he could test the drug against the human polio virus.

Sanders began his study in September 1947. A highly infectious and paralytic virus was injected into Swiss mice and allowed to grow for 24 hours. Half the mice

in the test group got simple salt water injections while the others were given pheno sulphazole injections four times a day. The drug saved up to 75 per cent of the animals treated while the untreated animals all died. Oral doses were also effective. The survivors were immune to reinfection, Sanders said in a paper he sent in June 1948 to ***Texas Reports of Biology and Medicine.*** Sanders now began investigation of pheno-sulphazole against a strain of the human polio virus in his colony of Rhesus monkeys.

A "ranking health official" in Texas became aware of Sanders report on Swiss mice and requested that pheno sulphazole be tested in the polio epidemic then taking heavy toll in the Galveston area of his state.

SubbaRow was not yet ready for clinical trials but sent Dr. Paul A. Eichorn, his assistant, with Sanders to Galveston and Houston in Texas for a spot study. Dr. Clifford Grulee of John Sealy Hospital's polio unit at Galveston and Dr. Paul Harrington of Jefferson Hospital's polio unit at Houston were interested in the animal data taken by Sanders. Dr. Chauncey Leake, Dean of University of Texas Medical School at Galveston, was willing to carry out pharmacological

studies.

Despite the "tenuousness of the data", SubbaRow was forced to give the green signal for the trial of pheno sulphazole in the polio epidemic because of the alarming reports of the toll Sanders and Eichorn brought back. He flew to Texas with Sanders and Eichorn on June 27 and worked out treatment schedules and other details with Drs. Leake, Grulee and Harrington.

Newspaper reporters who got scent of this were told to wait till a New York medical conference on July 12 and were sent off without any inkling about the trial being given to the drug in the polio hit population. The New York conference was later put off to August 23 but the whole story got into the newspapers on July 17. The newsagency UP had its sources in Columbia College and its rival AP buttonholed Dean Leake on a visit to California. Medical circles were scandalised when Science Service came out with a story that the "chemical conquest of virus diseases is . . . heralded by a chemical that stops infantile paralysis (polio)". Sanders issued a statement saying that he had not permitted any publication of scientific data and that it was impossible to say yet what beneficial results have been brought

about by the clinical application of the antiviral substance.

Despite this disclaimer, the stage was set for the trial of pheno sulphazole in the full glare of newspaper and public attention. Newspapers reported that more than 40 polio victims had been treated with two drugs and those who had received pheno sulphazole were up and walking around and that the acute illness period was being cut by a quarter from the usual five to eight days. Sanders began to be lionised, planned to leave Columbia and went to Florida on July 29 to discuss establishment of a virus research laboratory at Pratt General Hospital in Miami.

SubbaRow, who kept himself in the background, read with satisfaction reports by Sanders about his monkey experiments and by Dr. Harrington about clinical trials at Houston.

Monkey trials were less striking than mice results but were nevertheless “favourable”. Of the 79 given pheno-sulphazole among the 286 patients admitted to the Jefferson Davis Hospital, only one died and another showed residual paralysis. Thirteen of the 207 who did not get the drug died.

SubbaRow passed away on August 9 not suspecting that pheno-sulphazole was heading for an anticlimax. Both the animal studies of Sanders and the clinical findings of Harrington turned out to be exceptional experiences. The Grulee group at Galveston said on October 23 that the drug had been ineffective in the 13 patients to whom it was administered among the 31 admitted in the John Sealy Hospital. Similar reports came from hospitals in Cleveland, Ohio, Washington DC and Milwaukee, Wisconsin.

The consensus of the polio physicians attending a meeting convened at White Sulphur Springs, West Virginia, in October 1948 by the National Foundation for Infantile Paralysis was that pheno-sulphazole had not proved of value in polio. Virus research groups said the drug made no difference to mice infected with the polio virus. Carl Jungeblut at Columbia and Herald Cox at Pearl River repeated the mice and monkey experiments of Sanders and said they could not confirm his claim.

Murray Sanders remains convinced however that a promising drug was the victim of “intra corporate competition” and had been nullified by “careless”

attempts at confirmation of his animal experiments.

# End of the Quest for Panacea

ALONG with pheno sulphazole on trial in the Texas polio epidemic of 1948 was an antibiotic called Aureomycin. It too did not make the grade in the fight against the crippling disease but it was one of the first drugs to be effective against viruses and rickettsiae. Rickettsiae occupy a position between viruses and bacteria.

The discovery and development of Aureomycin came from a screening programme SubbaRow instituted in the spring of 1944 simultaneously with the programme that got him Hetrazan. It was an antibiotic SubbaRow had acquired with the help of "amateurs", men with no preconceived ideas who investigated the unknown with a truly scientific spirit.

SubbaRow had by then completed his work on fermentation and isolation of penicillin and wanted to look for sources of new antibiotics. Since filamentous moulds, Aspergilli and Penicillia, had all been surveyed extensively, he wished to institute a more thorough examination of Actinomycetes. Actinomycetes

are close to bacteria in appearance but resemble fungi in their growth. His decision was influenced by the recent announcement of streptomycin obtained from an actinomycete and by the feeling that bacteria had not received due attention as antibiotic producers because penicillin had overshadowed gramicidin.

SubbaRow got his first amateur when he looked for a plant physiologist for his antibiotic screening programme. Remembering his pleasant meeting with an old plant physiologist at the University of Wisconsin, he asked Ed Backus on his mycology group to write to his brother at Madison to meet the professor and secure the services of one of his students. Benjamin

Minge Duggar, when approached by the elder Backus, said his own services were available for SubbaRow. A distinguished authority on fungus diseases of plants, he had retired some six months earlier with the reputation as one who had made mushroom cultivation in the United States independent of European spawn.

SubbaRow had reservations about "prima donnas" but was touched by the fact that Duggar had to retire because of the age rule. Duggar was not only active but anxious to dedicate the evening of his life to something of more significance to human welfare than mushroom cultivation. He was willing to screen plant extracts and mould broths. It was a job he had never done before and he would not be handicapped by experience and theories.

Duggar came over on April 1, 1944. He began to screen soil and other samples received from everywhere. He prefixed A to code numbers for actinomycetes that he isolated and B for bacteria.

His first break came with B-71, the 71st bacterial isolate, found in a sample of Colorado soil. To let Duggar concentrate on actinomycetes, SubbaRow handed over the isolate identified as ***Bacillus polymyxa*** to John Porter, a mycologist on his staff. Porter and his associates were able to secure from this the antibiotic polymyxin. Polymyxin was found by physicians to be effective against undulant fever, whooping cough and meningitis. But SubbaRow withdrew it as it was somewhat harmful to kidneys. Meanwhile in August 1945, Duggar noticed a beautiful growth on agar in test tubes to which he had transferred actinomycetes

isolated from some University of Missouri soil samples. The conspicuous grey brown spores at the top were followed by a pink and a white zone ending in a moist golden area at the bottom. On agar plates, the actinomycete produced an antibiotic which arrested the growth of a broad spectrum of deadly disease germs - those susceptible as well as those resistant to the then known sulphas and antibiotics.

Exciting as the versatility of A-377 (the 377th actinomycete isolated), Duggar was disappointed it was not active against the tubercle germ. An anti TB drug more potent but safer than streptomycin was one of the objectives set for him.

So when he sent A-377 along with other promising actinomycetes to Edwin Ball for fermenting antibiotics in bottles, Duggar expressed his real enthusiasm for A-491 which had given a very sharp zone against the tubercle germ in agar plates.

SubbaRow did not share Duggar's enthusiasm when the report came from the bacteriology group on Ball's mould broths. They were having deaths with animals to which A-491 injections had been given. Right away, he realised it was nothing to fool with. It cleared the

lungs of tuberculosis but itself killed the animals.

He was on the other hand very happy when six guinea pigs which should have been dead with deadly germs injected into them were all alive because they had been given the partially purified A-377 broth.

Deciding that further work should be with A-377, SubbaRow picked up another amateur to solve the first of many production problems he would now face. Joseph Niedercorn was a synthetic chemist who had protested, “What do I know about microbes?”, when he was asked earlier to join the fermentation group. SubbaRow had then settled the issue by telling him that he could learn, and now silenced him by saying, “You can at least try,” when Niedercorn protested about the assignment to grow the yellow mould in five gallon stirred bottles. This was June 1946.

The yellow mould turned out to be quite individualistic. It was so unlike penicillin and streptomycin moulds in the manner it produced the antibiotic, and experience with the production of earlier antibiotics served as no guide. It virtually killed itself with the antibiotic it produced in the medium found so suitable for penicillin production. For in that medium the mould also produced lactic acid which combined with the antibiotic

to form a salt that got dissolved in the medium and destroyed the mould mycelia. Whereas the penicillin medium had to be kept slightly acidic for that antibiotic to remain stable, the A-377 medium had clearly to be neutralised to prevent the antibiotic dissolving in the medium and attacking the mould. But the neutralisation of the medium was not done because antibiotic production was supposed to have gone up by ten per cent earlier when the medium was acidified.

Niedercorn tried every possible change in the nutritional composition of the medium and as weeks passed he accumulated — a great deal of statistics on how much is produced in what medium.

When Niedercorn did not take the hint from his indifference to statistical experiments, SubbaRow lost temper and scolded him in the presence of assistants: "If you want to do those statistics, sit down with Dr. Albert Einstein." He refused to read any report with statistics and sent them all back to Niedercorn with a big "X" on them.

Niedercorn was forced to make a more systematic study of the mould's nutrition, discovered what was happening in the medium and found high antibiotic

concentrations in the medium when it was neutralised or made alkaline. He got a precipitate on February 26, 1947 when he added calcium carbonate (lime water) to the medium. The antibiotic formed- an insoluble calcium salt, and the mould lived longer to produce more antibiotic.

Before moving on to production in big tanks, SubbaRow had to choose between A-377 and five other yellow moulds all of which produced the antibiotic more or less equally well in Niedercorn's five gallon bottles. The choice was ultimately between A-377 and A-406. A-406 showed some toxicity in egg embryo experiments. SubbaRow decided on A-377 despite its inactivity against the tubercle germ when Ed Backus reported that it was more responsive to mutations. He remembered how artificial strains of ***Penicillium chrysogenum*** produced by mutation had helped boost penicillin production. Backus came up with a mould strain, A-377-899 (the 899$^{th}$ mutant), which produced two to three times more antibiotic than the natural mould, and his A-377- 2920-3 produced 15 times more antibiotic.

The pilot antibiotic plant got ready within SubbaRow's

department in April 1947. It took a year to straighten out problems in recovering the antibiotic from the fermentation mash and isolating the pure antibiotic in crystalline form.

Charles Pidacks, who was given the task of making a solvent extract of the antibiotic from the wet cake taken out of fermentation tanks, was an organic chemist but had worked for a while on penicillin and streptomycin purification. He could not quite cope with the procedures and his yields of the new antibiotic were poor. SubbaRow brought in George Krupka, his personal hatchet man, and he was able to boost yields by salting the antibiotic with sodium chloride into acetone. The addition of equal volumes of acetone and sodium chloride forced the antibiotic into the acetone layer.

The next step in purification was effected when the antibiotic was separated from water insoluble material in the fermentation mash by addition of hydrochloric acid.

The hydrochloride of the antibiotic thus obtained was still amorphous with lot of ash in it. Try as he did, Pidacks could not get rid of the ash.

SubbaRow was in the mean time in a desperate battle with the management to save the antibiotic project. One of the big Cyanamid executives wanted SubbaRow to scrap this single most expensive project on his research programme because money supply was tight with the country going through an economic recession. SubbaRow fought the suggestion like a bear and persuaded Bell to let him keep the project going by promising that everyone would work harder on new discoveries that would make more money for the company.

But it looked for a while as though the unpleasant task had to be done. They could not get the near pure product to crystallize, and SubbaRow gave his men just two weeks more. “Either we get it or we drop it,” he said bringing Krupka back into the Pidacks’s group. Krupka found the solution in just four days. He used picric acid to get the pure antibiotic and Pidacks put it in alcohol, and it crystallised.

SubbaRow was there that night on the first floor of Building 100 when under the microscope they got the first indication that the antibiotic was crystallising. They spent rest of the night working and left for home at dawn

when finally it went into gram quantities, leaving everything in the cold room for crystallisation to complete.

By then A-377 had been pronounced safe by the pharmacologists. Testing a material that was only 25 per cent pure, they found that oral doses produced almost no side reactions in animals. It however created irritation and inflammation at the site of injections. When the pharmacologists began shaking their heads, Krupka asked, “Well, why don’t you give it by mouth?” SubbaRow said light heartedly, “The physician will not allow it. He’s got to get his five dollars for the injection.” Once its wide-ranging action was proven, physicians were not slow in prescribing A-377. But physician acceptance of the new antibiotic at that time, when penicillin injections were in wide practice, appeared to be difficult.

SubbaRow initiated another series of animal trials. A-377 was effective against the typhoid paratyphoid group of microbes as well as erysipelas infection which had killed his only child. But could it match a rival company claim that it had an antibiotic which was active against viral and rickettsial infections? Harold Cox and

his associates said yes. It was effective against viral pneumonia and a venereal disease caused by a virus when tested in mice and guinea pigs. It also controlled rickettsial diseases like the "Q" and the spotted fevers. SubbaRow took A-377 in November 1947 to Johns Hopkins University's Perrin Long who was the first to recognise the merit of sulpha drugs in wound infections, had supervised wartime clinical testing of penicillin and was currently giving polymyxin its clinical trial. Test-tube and animal studies in Johns Hopkins department of preventive medicine and paediatrics of A-377's action against bacterial infections were discouraging. Dr. Long did not share SubbaRow's faith in A-377 and his belief that the new antibiotic might be more successful against infections in man.

SubbaRow therefore decided to have the viricidal properties of A-377 tested. He invited to Pearl River the distinguished Negro surgeon, Louis Tomkins Wright, and discussed with him Herald Cox's reports on the antibiotic's effectiveness against viral and rickettsial infections of animals. Dr. Wright was impressed and agreed to test it at his Harlem Hospital in New York in patients suffering from the viral venereal

disease called lymphogranuloma venereum (LV).

The clinical trial of A-377 began on January 22, 1948. Twenty five patients received the antibiotic and showed astonishingly fast disappearance of symptoms. Fourteen cases followed for two to sixteen weeks showed no relapse.

Returning from Harlem, SubbaRow called the boys who had worked on A-377 and announced: "We have a million dollar drug." He wished to share his happiness over the subjugation of a viral disease with those whose dedicated work had saved A-377 from the dust bin. The management had to wait till the next day for the news.

The mysterious "Q" fever broke out in a big way in California in May, and A-377 effected some dramatic cures of this rickettsial infection.

SubbaRow went with these clinical reports again to Johns Hopkins and Dr. Long was now willing to listen to him since he was disturbed by the high incidence of toxic reactions he was having with streptomycin.

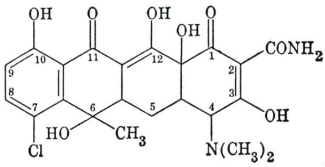
Johns Hopkins doctors first used A-377 in persons suffering from rickettsial diseases and got dramatic cures of the Rocky Mountain spotted fever. They were emboldened to try it in undulant fever, an occupational

disease among butchers. A-377 succeeded where other drugs had earlier failed.

SubbaRow then went to Boston City Hospital and gave the antibiotic to Dr. Maxwell Finland who first tried it in the test tube against 186 strains of disease germs isolated from patients. It was effective against many of them including those resistant to penicillin and streptomycin. Finland and associate physicians gave A-377 by mouth to a hundred patients suffering from a variety of bacterial infections. It exerted "a definite beneficial effect" in many bacterial diseases.

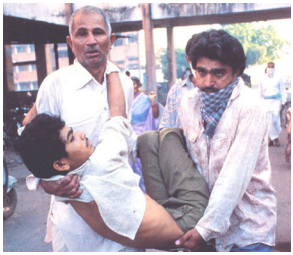
Drug trade journals got scent of these clinical trials and began to complain about "this bad man SubbaRow" who would not tell them anything about his new antibiotic.

By now SubbaRow had enough data from his frontal attack on the entire field of infectious diseases and set July 21 as the date for unveiling the drug before the medical world at a conference in New York City.




Duggar had long since identified A-377 mould as a member of the same

streptomyces group of actinomycetes to which the streptomycin mould belonged. He named it ***Streptomyces aureofaciens*** or the golden mould. The antibiotic it produced was named "Aureomycin" the golden antibiotic. The antibiotic crystals were golden yellow in colour, and Aureomycin heralded a golden era in the history of antibiotics.



Aureomycin was the first of tetracycline antibiotics, which have cut down the need for hospitalisation in many cases because they can be taken by mouth and have made elaborate laboratory tests unnecessary because they check any of a wide range of bacterial, rickettsial and viral diseases.

Aureomycin is chlortetracycline because it has a chlorine atom hooked to the tetracycline molecule. Tetracyclines as a group are the nearest things to the "panacea" – universal remedy – that SubbaRow sought. After its release to the medical world, Aureomycin was sent to the Haffkine Institute in Bombay (now Mumbai). There Dr. Sahib Singh Sokhey was able to save nine out of ten experimental animals suffering from septicaemia

caused by the plague germ *Pasteurella pestis*. Aureomycin proved itself in a plague case later that year in the American state of Arizona. It cured 12 of the 15 afflicted in the 1951 Latur (Hyderabad ) plague epidemic the other three being in such a critical condition that the drug had no time to act. Tetracyclines were therefore ready for the plague in Latur (now in Maharashtra) and Surat (Gujarat) in 1994. They arrested the epidemic and are credited with preventing its spread to other parts of India. SubbaRow thereby paid his debt to the Motherland in his centenary year. There was some debate whether the 1994 epidemic was plague or falciparum malaria but tetracyclines, particularly Doxycycline the third generation tetracycline, fight both the diseases. Doxycycline has been cleared by the US Food and Drug Agency (FDA) for prophylaxis of malaria, especially the malignant variety caused by *Plasmodium falciparum.*

# Picture of the Scientist as an Outsider

"SUB'S BOYS" with all these vitamins, antibiotics and other drugs not all of which have been described here wrote a glorious chapter in the history of pharmaceutical research. They had all been guided and inspired by SubbaRow and the best in them brought out by that particular knack SubbaRow had and by the paternal devotion and concern with which he nursed their talents and their personal welfare.

Some resented what they regarded as interference in their personal affairs by his demand that they work at night and on weekends and holidays. But all of them sooner or later developed a loyalty to his goals if not to him personally.

There are few parallels in American industry where a man with an alien cultural background and a scientist with an ingrained academic spirit was such a personal, administrative and research success as SubbaRow.

SubbaRow's greatness lay in his achieving a measure of communion with the people he worked amidst without either renouncing his cultural heritage or

sacrificing his scientific spirit.

SubbaRow did not stop being a “father figure” in the laboratory. He struck personal equations with many members of his team. He inspired such a filial devotion in Merton Lockhart, his partner in liver extract work, that Lockhart kept his ashes in an urn at his home to the last of his days. The way he “pampered and punished” Sam Kushner, who synthesized Hetrazan, led to a “love hate” relationship between the two. George Krupka, a janitor trained by him to be a top class isolation chemist, had lost his father when young and always said SubbaRow was “like a father to me”.

SubbaRow once took the children of Krupka to bowling. He was hurt when he was included in the bowling team only to be dropped the next day by the manager since bowling was open only to the “Caucasian race”.

He very much wanted Americans to accept him as one of them and some at Pearl River believe his friendship for an American woman in his laboratory was aimed at being recognised as an American by marriage. Miss Doris McKenzie was a medical technician with an impressive list of credentials and was taken as an assistant in the bacteriology group because nobody

believed in her ability. She proved herself when she got temporary charge of the group. SubbaRow tried to make up for his initial misjudgement of her. He raised her salary, put her in charge not only of the group which screened anti TB drugs but the cancer screening group and gave her whatever her laboratory needed.

SubbaRow and Doris were seen occasionally having dinner at various eating places. They began attending the same Emmanuel Baptist Church every Sunday at the nearby town of Ridgewood.

He had arrived in the United State a confirmed atheist, having renounced Adwaita in his medical college days, but his interest in religion was revived in the 30's. He was intrigued by the fact that "liquid crystals" — nitrogenous compounds with flat molecules that set themselves up in water medium like a deck of cards tossed into air closely resemble living cells but lack the attributes of living things. He was struck by the "philosophical necessity" to assume that life came from outer space to activate chemical molecules resembling liquid crystals.

He was at that time attracted to the sermons in Boston of Dr. John Haynes Holmes, the Unitarian minister who

helped make Mahatma Gandhi a beloved name to many Americans. The two exchanged letters on Christian doctrines. When Holmes built his Community Church in New York, SubbaRow contributed the "John Haynes Holmes Pulpit" in honour of Mahatma Gandhi.

SubbaRow signed on June 15, 1947 the Bond of Union of the Community Church. This was not an acknowledgement of Christianity by SubbaRow. For Holmes's was "a free church" with people from "all the great traditions" among its members who enjoyed full freedom of worship.

Doris McKenzie was a devout Christian and was the only person in the laboratory with whom SubbaRow could discuss religion. Learning of SubbaRow's membership of the Community Church, she set herself the task of winning him completely for Christ. She brought Gordon M. Torgersen, pastor of the Emmanuel Baptist Church of nearby Ridgewood, to Lederle Laboratories. Torgersen and SubbaRow discussed religion in letters and at informal get-togethers. A couple of months after SubbaRow began attending his Sunday sermons, Torgersen asked if he would "unite with our church". SubbaRow said he would if the invitation was

made in the spirit of George Truett, a great Baptist, who held that "all people who truly believe in Christ as their personal saviour are our brothers in common salvation whether they be in the Catholic communion or in a protestant communion or in any other communion or in no communion". For, SubbaRow wrote in a four page letter, "I am leading up to self priesthood. In this struggle, an intermediary priest or pastor has no place and cannot help."

SubbaRow had previously helped a nephew of McKenzie to go to college and he now extended financial support to the "Christian education" programme of Torgersen's church.

The same eagerness to identify himself with the community he lived in without renouncing his heritage influenced SubbaRow's attitude to citizenship.

Eight months before SubbaRow landed in New York in 1923, the American Supreme Court had ruled that Hindu Indians were not Caucasians whatever might be their race from a purely biological point and the President of the United States issued in 1924 a proclamation excluding Indians from American citizenship.

SubbaRow could get his original "student visa"

periodically extended because his scientific contributions were considered valuable to the United States. He was nevertheless afraid of being picked for some minor violation of the law and shipped back to India. When the Second World War broke out, he was required to carry an "alien registration card" bearing his right index finger impression, signature and the number 3420564. A thorough investigation of his record was made in 1942 before he was given special security clearance to continue as director of research at Lederle which had many sensitive defence contracts.

There were other Indian scientists doing valuable work at this time in the United States, and many Congressmen and Senators among others considered it unfair to deny them citizenship while taking advantage of their inventions and discoveries which were helping win the War. But it was only on July 2, 1946 that a law came into force lifting the bar on Indians getting American citizenship.

SubbaRow was human enough to wish to shed his alien status. Moreover, difficulties were developing at this time for the continued residence of foreigners in the United States.

SubbaRow therefore approached the New York office

of the Immigration and Naturalization Service which ruled on July 18, 1947 that he was a legal immigrant. When SubbaRow spread the happy news, his associates at Pearl River thought that he had received his first citizenship papers and would be granted citizenship on his completing formalities. But he never even filed his "Declaration of Intention" two years after which he could have formally sought citizenship. Filing the declaration would have been out of character for a scientist who recognised no national ties but only obligations to humanity. An aspiring world citizen could not give up one national identification to acquire another.

If SubbaRow had any weakness it was his unwillingness to admit that anyone was superior to him just because he was an American. Krupka recalls how, when Cox would not agree to join his anti polio programme, SubbaRow learnt in a week all there was to know about viruses and started his own independent virus group. It was this trait in him that made SubbaRow take up all sorts of challenges and try his hand at many sports boxing, bowling, tennis, golf, archery, swimming, horse back riding. He flitted from one sport to another after

attaining mastery. He gave up archery because the wind toppled and broke the target. His indulgence in sport was also a part of his effort to overcome his lack of muscle coordination which troubled him in such things as walking on streets covered with ice. He was prone to slip and fall and had to walk with care.

The acquisition of a car only added to his troubles. Because each of his moves was conscious and not an automatic reflex action, his driving was shocking. He decided in August 1945 to learn flying and see if it would improve his muscle coordination and help him in mental relaxation. Clyde Ervin, a former air force flight instructor, had recently joined his staff and agreed to give him lessons. They flew a Piper Cub evenings and weekends. They had a "close call" quite early in the training programme. The engine died when Ervin retarded the throttle while demonstrating a "stall". Ervin dived the plane toward the ground to gain enough speed for the wind to force the propeller to turn and start the engine. They were only 1200 feet above a cemetery when the plane levelled off. SubbaRow joked Ervin took him flying over the cemetery so that they would be planted there without trouble in case

something happened. After a little over a year of instructions, SubbaRow made his first solo flight, and got his coveted Private Pilot's Licence on October 15, 1947. He bought a personal Aeronca and Ervin accompanied him on most of the flights.

# Death of a Titan

AT eight on the morning of August 7, 1948 SubbaRow stood in front of his research building admiring the flowers. A mycologist passed by, was amused he was wearing a rain coat at summer time and moved on noticing he was lost in a reverie. Walking away, Clifford Hesseltine wondered if SubbaRow was contemplating the future or reviewing the past of his research department.

If it was the future, SubbaRow might have been thinking of the new laboratory facility at Wyckoff for an all out attack on cancer. Those who knew of his plans would say a few days later, "Ten more years and he would have had an answer to cancer."

In the unlikely event of it being the past, he might have been reviewing the previous ten months when an unbelievably large number of his projects had come to fruition: After a gap of nearly a year and a half between folic acid and Hetrazan, the pace had gathered momentum. Hetrazan was in October 1947, teropterin in December and aminopterin in April 1948. It was polymyxin in May and pheno-sulphazole trials in the Texas polio epidemic in June, and Aureomycin had been received with so much enthusiasm only a fortnight earlier.

Later that day, SubbaRow took off from Spring Valley in his Aeronca with Clyde Ervin and it was late when he returned to Spring Valley and drove back to Pearl River in his coupe. The next day was a Sunday, a working day like any other day, and he put in a full day at the laboratory. When he returned to the apartment house in the evening, he ran into Dr. Sam Thomas and his wife at the entrance. Mrs. Thomas taught mathematics in New York and SubbaRow always liked to chat with her because of their shared interest in mathematics.

After dressing for the night, he read the local newspaper, placed it and his reading glasses neatly on the bedside chair, switched off the light and went to sleep.

He was not in his laboratory on Monday morning. When he did not come in even by three in the afternoon, when an important conference was scheduled, his distraught secretary called him on the phone several times. There was no response from his apartment. Doris McKenzie sent Luke Malone, an associate, who found SubbaRow's car in the garage. Malone was sent back with Leo Rane, the bacteriologist, who had the apartment opened and

found SubbaRow dead in his bed.

Malcolm, Lockhart and Doris McKenzie were all quite shaken when they came in. Doris spoke for all of them: "How little he asked for himself during life!"

The word of SubbaRow's death — so sudden and least expected — spread from laboratory to laboratory at Pearl River after Miss Sybella Halliday received Rane's phone call and rushed to Doris McKenzie with tears rolling down her cheek. Even laboratory technicians who had not worked directly for him felt bad about the death of one who was, they were sure, kept by the management only because of the worth of his contributions.

Coy Waller was so disturbed that he wanted to cancel his trip that night to San Francisco where he and Boothe were to present papers on the folic acid conjugates and antagonists. He went when people said SubbaRow was so dedicated to scientific effort that he would have wished him to go.

Frank Ablondi who had worked for SubbaRow was dumbfounded. SubbaRow had never complained about heart or anything and they thought of all sorts of things. But the postmortem report was: Death due to

heart attack. This inspired romantic stories about how SubbaRow had driven himself and his men because he knew his heart condition and thought he had only ten years ( the then life expectancy of heart patients) to accomplish his work on earth.

They all paid their respects at private services held on August 11 in a funeral parlour.

The next day however Gordon Torgersen, summoned back by Doris McKenzie from New Hampshire, insisted on a full funeral service at the Ridgewood church. Three hundred persons attended. There were of course drug company executives, scientists and technicians as well as men from the academic world. But it was so much a parish affair that one friend from the Harvard days asked himself how had SubbaRow filled the church with so many. He could not understand why the women were crying.

Torgersen chose as the text of his sermon the words with which Jesus Christ on the cross had been taunted: "He saved others; himself he cannot save." He movingly spoke of SubbaRow who had helped save so many lives but could not save himself from the killer who had struck while he slept at peace with the world.

It is quite common for pastors to include in sermons a plea for support to Church activities and call for contributions. The young Mr. Torgersen did not

however take into consideration the sensitivity of those in the congregation who were devoted to SubbaRow when toward the end of his funeral oration he asked for contributions to the Church's educational activities until then handsomely supported by SubbaRow. Sam Kushner was outraged and when the coffin was carried out wept for the first time after he became an adult.

The Rockland County as well as the New York City newspapers carried obituary notices that were surprisingly big for a scientist who had shunned the limelight in his lifetime.

Vilma, now a medical librarian in a west coast university, was notified by a friend and retired for a few days into solitude at Laguna Beach with the "Legacy of India" and "Bhagavad Gita" he had given her during the Boston days.

Venkamma received Malcolm's wire at Kakinada where she lived with Annapurna. She had hopefully asked about her son's return from everyone who had met him in the States. She was now inconsolable, could not understand how she had outlived her son. She got an idea of his achievements in the far off land from a letter Malcolm later wrote, and she unveiled a few years

later a memorial plaque to SubbaRow at Lederle's plant in Gujarat manufacturing some of the products of his research.

Annapurna's son sent to Anaparthi a clerk who could go only half way because the train engine developed trouble. His wire reached late in the night and Seshagiri, woken up, swooned when it was read out. She learnt weeks later that her marriage, which played such an important part in securing SubbaRow his opportunity, had after all not been annulled.

American Cyanamid, which reaped a golden harvest from tetracyclines, erected a plaque in honour of SubbaRow and built a library named after him in the campus of Lederle Laboratories.

A greater accolade to SubbaRow was the naming of a fungus as *Subbaromyces splendens* by its discoverer, Clifford Hesseltine, who had seen at close quarters how SubbaRow 'was unique in that he could take dreams and people and make reality'. Whereas this first species of the previously unknown genus was found in SubbaRow's *karmabhoomi* a sibling, *Subbaromyces aquatica,* was subsequently discovered in his *janmabhoomi* at Hyderabad by Manohara Chary and P Rama Rao.

The New York *Herald Tribune* it was which put in an editorial all that could be said of SubbaRow: He had been a commanding figure in medical research and many advances in modern medicine stood as monuments to his genius. He was one of the most eminent medical minds of the Twentieth Century!

# AFTERWORD

by

Rajesh Bhatnagar MD

## The Continuing Miracles of the Miracle Man's Miracle Drugs

DOCTOR YELLAPRAGADA SUBBAROW'S direction of research at Lederle Laboratories, Pearl River, New York, USA, led in the Nineteen Forties to the discovery of four medical molecules which opened new approaches to the treatment of nutritional, infectious, worm-transmitted diseases and cancer. Perhaps the count should be reduced to three because manipulation of a single molecule yielded first the vitamin folic acid and then the cancer fighter anti-folic methotrexate. The uniqueness of these molecules is that today, fifty years after their discovery, they are being still researched for potential new benefits to humankind.

Aureomycin, with the tetracycline molecules, was derived from the fungus *Streptomyces sp.* and proved for the first time that a single drug can be used for controlling infections caused by both gram-positive and gram-negative bacterial germs. The previously available penicillin could battle only the former and streptomycin only the latter. Also unlike penicillin and streptomycin, Aureomycin could be taken orally.

The second generation antibiotics with the tetracycline molecule helped eradicate the plague which broke out in Gujarat and Maharashtra just when SubbaRow's centenary year began in 1994. It was a debt SubbaRow paid to his motherland almost half a century after death which claimed him soon after the unveiling of Aureomycin before a medical gathering at the New York Academy of Sciences. People then said death was jealous of SubbaRow who was coming out with a new potent drug every year and was set to conquer cancer. Death, Be Not Proud! we can say with John Gunther. For the four molecules he presented to the world in four years continue to battle ever new diseases.

Aureomycin was sent soon after its medical release to the Haffkine Institute in Bombay (now Mumbai). There the famed Dr Sahib Singh Sokhey was able to save nine out of ten experimental animals suffering from septicaemia caused by the plague germ *Pasteurella pestis*. Sokhey incidentally was SubbaRow's senior at Harvard Medical School biochemistry department.

After Aureomycin proved itself in a plague case later that year in the American state of Arizona, it was tried in 1951 in Latur, a hyper-endemic plague area then in Hyderabad

state but became part of Maharashtra later. Of the 15 plague victims treated by Dr K Ramachandran at the Isolation Hospital, 12 were cured and discharged. The three who died had been brought in a serious condition and the drug had no time to act. Tetracycline was therefore ready for plague in Latur and Surat in 1994. It cannot resolve the debate whether the epidemic was plague or falciparum malaria as it, particularly Doxycycline, fights both the diseases.

Doxycycline, the third generation tetracycline, has now been cleared by the US Food and Drug Agency (FDA) for prophylaxis of malaria, especially the malignant variety caused by *Plasmodium falciparum*. Unlike the traditional chloroquine and the new mefloquin, Doxycycline is least toxic and is effective if taken just 24 hours before exposure. Mefloquin needs at least 7 days to impart immunity against malaria. In September 1999 when the United Nations Assistance Mission in East Timor (UNAMET) was ordered into the region wrested from Indonesia, its international staff packed Doxycycline in their survival kits.

Tetracycline is even today the only drug effective in Rickettsial group of diseases, like scrub typhus and the

Rocky Mountain spotted fever, known as the scourge of war because of the heavy toll they took of soldiers in the trenches of the First World War.

Folic acid, also fathered by SubbaRow, was initially used only for the treatment of tropical sprue and the anaemias. Recently, FDA approved it for expectant mothers and in fact recommended its regular use a month before planning progress to stave off neural tube defects. The U.S. government has required that all flour, pasta and other grain products manufactured after January 1, 1998 be enriched with folic acid. In mid-1999 the *New England Journal of Medicine* reported that this has already reduced homocysteine levels across the board among the U.S. population. The report started a worldwide debate focussing on homocysteine, an amino acid, as an independent risk factor for coronary artery diseases. It has been statistically seen that people with heart attacks fare poorly if they have also high homocysteine levels associated. Folic acid reduces these homocysteine levels and may improve the resistance of the general population to ischemic heart diseases.

Aminopterin, the third brainchild of SubbaRow, has the folic molecule with an amino radical replacing the hydroxy

radical in the vitamin. It reverses the vitamin action of folic acid and is called an anti-folic or folic acid antagonist. It provided for the first time some semblance of treatment for leukaemias. It initiated the chemotherapeutic approach to treat widespread cancers or cancers not amenable to surgery. Methotrexate the modified aminopterin has singly improved the survival of young women suffering from choriocarcinoma the cancer of the after-birth mimicking pregnancy.

In fact, methotrexate, used initially in cancer treatment, is finding a new place in non-cancerous diseases. It has become a fairly standard drug in treatment of rheumatoid arthritis and psoriasis, the two chronic disabling conditions of joints and skin.

Though needing further evaluation, methotrexate has been used successfully in chemotherapeutic treatment of ectopic pregnancy, chronic ulcerative diseases and asthma. It may prove to be a boon to asthmatics as it can reduce steroid dependency and thus the complications from the steroids.

Di-ethylcarbamazine, the fourth molecule that SubbaRow pioneered, has helped the afflicted nations fight the scourge of filaria which leads to the extremely disfiguring

elephantiasis disease. After years of hesitation in employing it in mass campaigns, although it has long been the only effective anti-filarial, it has now been cleared for prevention of filariasis on a mass scale in endemic areas. In an attempt to reduce the burden of the disease, WHO on Indian Republic Day 1998 said it was now enough to administer only a single dose of DEC, concurrently with ivermectin, to keep blood free of filarial worms for a whole year. It said the unpleasant side effects were due to unnecessarily high dosages previously prescribed.

There seems to be no end to such new SubbaRow miracles!

# CHRONOLOGY

12 January 1895 : Born in Bhimavaram, W. Godavari, Andhra Pradesh, India

1908 : Aborted attempt to run away to Varanasi

January 1913 : Father Jagannadham Dies

Joins Madras Presidency College

1915 : Enters Madras Medical College

10 May 1919 : Marries Seshagiri.

1921 : LMS Certificate

July 1921 : Brother Purushottam dies of Tropical Sprue

1921 : Lecturer in Anatomy and Physiology at Madras Ayurvedic College

27 September 1923 : Leaves Bombay for USA via London

26 October 1923 : Arrives in Boston to enter the Harvard School of Tropical Medicine

12 April 1924 : Son is born

I June 1924 : Diploma in Tropical Medicine

Enters Harvard Medical School for Ph.D. in Biochemistry

24 December 1924 : Son dies of Erysipelas

December 1925 : Fiske SubbaRow Method published in *Journal of Biological Chemistry*

April 1927 : Phosphocreatine unveiled before the Society of Biological Chemists at Rochester, N.Y.

August 1929 : ATP presented at the 13th International Physiological Congress

19 June 1930 : Harvard Ph.D.

Teaching Fellow, HMS

April 1934 : Vilma Prochownick joins SubbaRow's laboratory

6 June 1935 : Renounces credit for Phosphocreatine, ATP

1 September 1936 : Instructor

September 1937 : Vilma leaves SubbaRow's laboratory to enter Colorado Sanatorium

October 1938 : Associate

May 1940 : Leaves HMS

Associate Director of Research, Lederle Laboratories, Pearl River

9 September 1941 : Florey & Heatley visit Pearl River to get SubbaRow's Penicillin

24 January 1942 : Gramicidin produced as first-ever

antibiotic at SubbaRow's laboratory; is cleared for first aid dressings.

1 October 1942 : Director of Research

31 August 1945 : Folic Acid synthesis announced in *Science*

17 October 1947 : Hetrazan unveiled

April 1948 : Aminopterin's success in leukaemia announced

21 July 1948 : Aureomycin presented to the New York Academy of Sciences

9 August 1948 : Dies in sleep, Pearl River, NY, USA.

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डाक्टर येल्लाप्रगडा सुब्बाराव की अमर कहानी

**(SARV ROG NIVARINEE KEE KHOJ MEIN
DOCTOR YELLAPRAGADA SUBBAARAAV KEE
AMAR KAHANEE)**

Adaptation in Hindi by
Vinod Kumar Mishra

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## एक निवेदन

हम प्रोफेसर वाइ सुब्बाराव स्मारक गोष्टी (1994) आयोजन समिति से मिले अनुदान के लिए आभारी हैं। यह हमारे संपादक डाक्टर एस. एस. रस्तोगी तथा डाक्टर ए. के. अग्रवाल ने स्वीकार किया। इससे हमने इस पुस्तक का मूल्य वास्तविक मुद्रण शुल्क के अनुसार रखा है और हम अपनी शुभ कामनाओं के साथ पाठकों के सामने प्रस्तुत कर रहे हैं।

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